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Clinical efficacy of diquafosol sodium 3% versus hyaluronic acid 0.1% in patients with dry eye disease after cataract surgery: a protocol for a single-center, randomized controlled trial

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ABSTRACT

Introduction The number of cataract surgeries, the most common ophthalmic surgery, is expected to increase due to aging populations. Dry eye disease (DED) is a frequent side effect after cataract surgery, contributing to lower postoperative patient satisfaction and suboptimal quality of vision. It is unclear which eye drops commonly used in these patients should be recommended for postoperative DED treatment. This study aims to compare the efficacy of topical administration of diquafosol sodium 3% versus hyaluronic acid 0.1% eye drops in patients with DED after cataract surgery.

Methods and analysis The study is designed as a single-blind randomized controlled trial. The participant will be randomly (1:1) allocated to either the diquafosol sodium 3% topical administration group (n = 21) or the hyaluronic acid 0.1% topical administration group (n = 21). Each group will receive its assigned eye drop intervention over a 12-week period. The primary outcome will be measured using the total score of the Japanese version of the Ocular Surface Disease Index during the visit 5 weeks postoperatively. Both groups will be followed up after their respective eye drop application for 12 weeks according to the intervention regimens. Secondary outcome measures including meibomian gland function assessment, tear film break-up time, keratoconjunctival staining score, maximum blink interval, and tear secretion volume using Schirmer's test I will be assessed at 1, 5, 9, 13, and 25 weeks postoperatively.

Ethics and dissemination This study has been approved by the Juntendo Hospital Certified Review Board, Tokyo, Japan (approval number: J20-018) and was registered with the Japan Registry of Clinical Trials. Written informed consent will be collected from every patient prior to study participation. The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Trial registration number: jRCT1031210018

Strengths and limitations of this study

- This is the first single-blind, randomized controlled trial to compare the efficacy of topical administration of diquafosol sodium 3% versus hyaluronic acid 0.1% eye drops over 13 weeks in 42 patients with postoperative dry eye disease (DED) after cataract surgery with a 12-week follow-up period.
- Outcome measures include subjective symptoms of DED using the Japanese version of the Ocular Surface Disease Index (J-OSDI) questionnaire, meibomian gland function assessment, and dry eye examinations, including tear film break-up time, keratoconjunctival staining, maximum blink interval, and tear secretion volume.
- The primary outcome measure comprises patient-reported subjective symptoms of DED using the J-OSDI questionnaire at 5 weeks postoperatively.
- The trial findings will help inform health care providers and patients on the comparative effectiveness of the two most common eye drops prescribed for postoperative DED after cataract surgery.

INTRODUCTION

The number of cataract surgeries, the most common ophthalmic surgery, is expected to increase due to aging populations worldwide.[1] Cataract surgery is generally recognized as a safe, reproducible, and effective procedure, owing to improvements in surgical techniques and instruments.[2] Therefore, patients demand high postoperative quality of vision. Unfortunately, dry eye disease (DED) is a common and major cause of postoperative discomfort,[3] with recent studies revealing that cataract surgery is associated with the development and increased severity of dry eye symptoms.[4-7] In addition, DED has been shown to impair the quality of vision and increase economic losses due to reduced concentration and decreased work productivity stemming from a variety of DED-related symptoms, such as ocular discomfort and decreased visual acuity.[8, 9]

Importantly, contributory factors usually associated with DED differ from those implied in the development of DED after cataract surgery, which include the following: application of preoperative prophylactic medications; irritation of the ocular surface; application of topical anesthetics and antiseptics; intraoperative exposure to microscope light; corneal nerve transection; increased tear osmolarity; goblet cell loss; meibomian gland dysfunction; and surgery-related inflammation.[1, 4, 10-14] Moreover, numerous host factors including age, sex, presence of systemic diseases, administration of systemic medications, and preexisting DED or meibomian gland dysfunction are associated with the development of DED after cataract surgery.[1, 3, 4, 13, 15-22] The clinical presentation of postoperative DED caused by these various factors is also different from that usually seen in DED, therefore, requiring a specialized treatment strategy for DED after cataract surgery.

Although the importance of DED management after cataract surgery has been recognized and many options to treat DED after cataract surgery have been developed,[1, 17-19, 23-33] the choice of treatment is left to the discretion of each physician as no clear guidelines exist for the treatment of DED following cataract surgery. Diquafosol sodium 3% and hyaluronic acid 0.1% eye drops are two widely used medications for patients with DED.[34] There have been previous efforts to compare the effects of these eye drops after cataract surgery,[19, 23] but these studies targeted patients with preexisting DED. This highlights the need to assess the efficacy of various eye drop medications in patients that develop DED following cataract surgery.

To the best of our knowledge, no report has yet compared the efficacy of diquafosol sodium 3% and hyaluronic acid 0.1% for DED after cataract surgery in patients without preexisting DED. Therefore, this study's objective is to compare the efficacy of these eye drops for DED after cataract surgery in such patients.

METHODS AND ANALYSIS

Objectives

The primary objective is to compare the efficacy of topical administrations of diquafosol sodium 3% versus hyaluronic acid 0.1% to alleviate dry eye symptoms (measured using the Japanese version of the Ocular Surface Disease Index [J-OSDI]) after cataract surgery in patients without preexisting DED, as a therapy in addition to standard treatment following this operation.

Study design

The study is designed as a prospective, single-blind, randomized, controlled trial. The total number of participants will be 42 patients randomly allocated to the diquafosol sodium 3% administration group (n = 21) or the hyaluronic acid 0.1% administration group (n = 21). Each group will receive the assigned treatment over a 12-week period. A subsequent 12-week observation period from 13 to 24 weeks will be used to check for persistent eye drop effects and DED recurrence. The study design is depicted in figure 1.

Study setting

This study will be conducted between April 1st, 2021, and November 30th, 2025. Participants will be recruited at the Department of Ophthalmology, Juntendo University Hospital.[35]

Participant selection

This clinical trial will be conducted in a single center, with the participant blinded to the treatment allocation. Patients with DED after cataract surgery who attend the Department of Ophthalmology, Juntendo University Hospital, or are admitted to it are eligible for inclusion in this study.

Inclusion criteria

1. Women who are 20 years of age or older at the time of providing informed consent.
2. Patients who have undergone cataract surgery in both eyes, with the second operation within 14 days after completion of the first.
3. Patients diagnosed with DED after cataract surgery (> 13 points total score in the J-OSDI and tear film break-up time ≤ 5 s), according to the 2016 Asia Dry Eye Society criteria.[36]
4. Patients who, after receiving a full explanation of their participation in the study and with a full understanding of the study, have given written consent to participate in the study of their own free will.
5. In case of an inability to self-administer eye drops, patients with a caregiver willing and able to assist in the administration of the assigned eye drops as part of the study.

Exclusion criteria

1. Patients diagnosed with DED preoperatively.
2. Patients with active eye infections.
3. Venal keratoconjunctivitis patients.
4. Patients with recurrent corneal erosions.
5. Patients with hereditary corneal disease.
6. Patients with physical irritation of the cornea and conjunctiva due to eyelashes, tears,

or conjunctivochalasis.
7. Patients who cannot or will not be able to discontinue eye drops and medications listed as prohibited concomitant drugs (including all prescription and over-the-counter medications), beginning with the start of the screening test until the end of the administration of the study medication.
8. Patients who cannot discontinue the use of contact lenses in the inclusion period, between the start of the screening test and the last administration of the eye drops.
9. Patients with a history of corneal refractive surgery.
10. Patients with punctal plugs or a history of surgical punctal occlusions.
11. Patients with hypersensitivity to components of the study drugs and reagents.
12. Patients using glaucoma eye drops.
13. Any other patient whom the principal investigator deems unsuitable as a study participant.

Interventions

After enrollment in the study, participants will receive their corresponding study medication for the intervention period of 12 weeks after cataract surgery. The cataract surgery procedure entails an invasive corneal incision with a width of 2.4 mm. The conventional treatment up to 1 month after cataract surgery is gatifloxacin 0.3% ophthalmic solution instillation four times a day, betamethasone sodium phosphate 0.1% four times a day, and bromfenac sodium 0.1% twice a day. Successive treatment up to 3 months after surgery includes gatifloxacin 0.3% ophthalmic solution instillation four times a day, fluorometholone 0.1% instillation four times a day, and bromfenac sodium 0.1% instillation twice a day.

Arm A - diquafosol sodium 3% plus conventional treatment after cataract surgery
The participants will use diquafosol sodium 3% eye drops alongside conventional treatment after cataract surgery. Diquafosol sodium 3% eye drops will be administered six times a day.

Arm B - hyaluronic acid 0.1% plus conventional treatment after cataract surgery
The participants will use hyaluronic acid 0.1% eye drops alongside conventional treatment after cataract surgery. Hyaluronic acid 0.1% eye drops will be administered six times a day.

Outcome assessments

The schedule for data collection and visits is shown in table 1. Assessments will be performed following a predetermined sequence. After determining the subjective symptom score using the J-OSDI questionnaire, a physician will conduct a face-to-face medical examination and interview on lifestyle-related information. Following surgery, a wide range of ophthalmic examinations will be performed, including measurements of corrected vision, intraocular pressure, contrast sensitivity, corneal curvature radius, and corneal endothelial cell density. In-person slit-lamp microscopy and fundoscopy examination by a physician will follow shortly after. The physician will continue with dry-eye-related ocular function tests and evaluate tear film break-up time, fluorescein

staining score, maximum blink interval, and meibomian gland function. Subsequently, a trained nurse will measure the subject's tear production using Schirmer's test I. Patients will be provided with an individual patient diary that includes instructions for use, visit schedule, and how to use the eye drops. Patients reports include the number of times eye drops were administered per day, reasons for not administering the eye drops, any side effects, and use of new drugs other than investigational drugs of this study.

Table 1 Schedule for data collection and visits

Periods	Pre-observation period		Drug administration period (12 weeks)				Post-administration period (12 weeks)
	Before cataract surgery 0–3 months before cataract surgery	Cataract surgery	After cataract surgery				
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
		Week 0	Week 1	Week 5	Week 9	Week 13	Week 25
Informed consent and eligibility screening	○						
Registration to the study			○				
Randomization			○				
Participants' characteristics	○						
Lifestyle-related information	○		○	○	○	○	○
Ophthalmic examinations							
Visual acuity	○		○	○	○	○	○
Intraocular pressure	○		○	○	○	○	○

Contrast sensitivity	○		○	○	○	○	○
Keratometry	○		○	○	○	○	○
Endothelial cell count measurement	○		○	○	○	○	○
Slit-lamp microscopy	○		○	○	○	○	○
Fundus examination	○		○	○	○	○	○
Cataract surgery		○					
Postoperative eye drops for cataract surgery		○	○	○	○	○	○
Information about cataract surgery		○					
Subjective symptoms of dry eye (J-OSDI)	○		○	○	○	○	○
Meibomian gland function assessment	○		○	○	○	○	○
Dry eye examination							
Tear film break-up time	○		○	○	○	○	○
Keratoconjunctival vital staining	○		○	○	○	○	○
Maximum blink interval	○		○	○	○	○	○
Tear secretion volume using	○		○	○	○	○	○

Schirmer's test I						
Treatment: diquafosol sodium 3% or hyaluronic acid 0.1%, 6 times per day		○	○	○	○	
Adverse event collection		○	○	○	○	○
Patient diary	○	○	○	○	○	○

J-OSDI, Japanese version of the Ocular Surface Disease Index.

Primary outcome

Japanese version of the Ocular Surface Disease Index

The primary outcome measure will be the scores in the Ocular Surface Disease Index, which is a questionnaire consisting of 12 questions for evaluating the effects of dry eye syndrome on vision, ocular symptoms, and any condition associated with DED.[37] The J-OSDI, the Japanese version of this index, has been validated and will be used for this study.[38] The patient will answer each question on a scale ranging from 0 to 4, with 0 indicating 'none of the time' and 4 indicating 'all of the time'. If a certain question is deemed irrelevant, it will be marked as 'not applicable (N/A)' and excluded from the analysis. The J-OSDI total score is calculated according to the following formula.[37, 38]

$$\text{J}-\text{OSDI total score} = \frac{(\text{Sum of scores for all questions answered}) \times 100}{(\text{Total number of questions answered}) \times 4}$$

The scale ranges from 0 to 100, with higher scores representing more severe cases of DED. This value will be checked during visits preoperatively and 1 week, 5 weeks, 9 weeks, 13 weeks, and 25 weeks postoperatively.

Secondary outcomes

Secondary outcomes will be largely categorized into five groups: 1) general characteristics and relevant medical history, 2) lifestyle factors, 3) ophthalmic examination, 4) surgical information, and 5) ocular function tests.

Participants will provide characteristics including age, sex, diagnosis, and relevant medical history regarding the use of contact lenses, increased intraocular pressure, ocular surgery, corneal disease, mental illness, and hay fever. Information on lifestyle

factors will contain self-reported headache, stiffness, screen time, sleep duration, exercise, smoking, and sleeping pills. Examination results on corrected visual acuity, intraocular pressure, contrast sensitivity, keratometry, endothelial cell count measurement, slit-lamp microscopy, and fundus examination will also be analyzed. Various surgical information that pertains to the cataract surgery, including surgical procedure, surgery time, complications, and information about the surgeon, will be collected for analysis.

Specific function test results on meibomian gland function and dry eye examinations will be collected and analyzed as well, including tear film break-up time (TFBUT), keratoconjunctival vital staining (CFS), maximum blink interval (MBI), and tear secretion volume according to the Schirmer's test I.

Outcomes that pertain to repeatable examinations or function tests will be measured during the preoperative visit, as well as during postoperative visits in weeks 1, 5, 9, 13, and 25.

Meibomian gland function assessment

Meibomian gland function will be assessed by applying digital pressure onto the lower central eyelid, in conjunction with slit-lamp microscopy according to the standard method.[39] Abnormal findings around the orifices are considered positive when at least one of three findings (irregular lid margin, vascular engorgement, and anterior or posterior replacement of the mucocutaneous junction) is recognized. Findings indicating orifice obstruction will be judged positive when both findings indicating meibomian gland orifice obstruction (plugging, pouting, and ridging, decreased meibomian secretion) are recognized.

Tear film break-up time

TFBUT will be measured using a fluorescein dye according to the standard method.[36] To minimize any effects of the test strip on tear volume and TFBUT, a small quantity of the dye will be administered with a wetted fluorescein strip. After the dye is instilled, the subject will be instructed to blink three times to ensure adequate mixing of the dye with the tears. The time interval between the last blink and the appearance of the first dark spot on the cornea will be measured with a stopwatch. The mean value of three measurements will be used. The cutoff value of TFBUT $\leq$ 5 s will be used to diagnose DED.[36]

Keratoconjunctival vital staining

CFS will be graded according to the van Bijsterveld grading system,[40] dividing the ocular surface into three zones: nasal bulbar conjunctiva, temporal bulbar conjunctiva, and cornea. Each zone will be evaluated on a scale of 0–3, with 0 indicating no staining and 3 indicating confluent staining. The maximum possible score is 9.

Maximum blink interval

MBI will be defined as the length of time that the participant can keep the eye open before blinking during each trial.[41] According to previous studies,[41, 42] Using a stopwatch, MBI will be measured twice under a light microscope without light. MBI will be recorded as 30 s if it exceeds this value. The cutoff value of MBI ≤ 12.4 s will be used as a positive sign for DED.

Tear secretion volume using Schirmer's test I

Schirmer's test I will be performed without topical anesthesia after the completion of all other examinations. Schirmer test strips (Ayumi Pharmaceutical Co., Tokyo, Japan) will be placed at the outer third of the temporal lower conjunctival fornix for 5 min. The strips will be removed, and the length of dampened filter paper (in mm) will be recorded.

Participant timeline and trial duration

The schedule for data collection and visits is shown in table 1. After registration to this study, the assigned treatment intervention will be administered for 12 weeks. Furthermore, the sustained effect of eye drops and the recurrence of DED will be examined during the 12-week follow-up period 13–25 weeks after surgery.

Randomization and allocation

Participants will be randomized to the diquafosol sodium 3% administration group or the hyaluronic acid 0.1% administration group. Randomization will be performed by a member of the trial team on the day of the visit 1 week after cataract surgery. A web-based randomization application will be used (https://www.project-redcap.org/). Allocation will be carried out using block randomization and stratified according to age (allocation factor: age < 80 years or ≥ 80 years). A randomization list for each stratum will be prepared by an independent statistician and will be stored in the university data center.

Masking

Study treatment assignment is single masked. The study participants are unable to identify the contents. Labels on the box containing the ampoules have a batch number, study reference number, participant ID, contact number, investigator name, site address, expiration date of the eye drops, storage instructions, and a statement informing the participant that the eye drops are for clinical trial use only and are not to be ingested.

Compliance

The study is to be conducted using an intention-to-treat basis. The level of compliance with eye drop use will be quantified based on the eye drop use calendar. There is no

minimum compliance criterion for eye drop insertion that would cause the removal from the trial, but compliance will be controlled for in statistical analyses and used as a measure of acceptability of the treatment according to the secondary objectives. Evidence of overuse will also be discussed with participants, and they will be re-instructed on proper use and compliance.

Sample size and statistical analyses

The target number of cases is set at 42. The breakdown is as follows. First, a t-test for difference of means (power 0.8, significance level 5%, clinically valid difference in subjective symptom score 5.24,[23] standard deviation of the comparison group 5.23[23]) was used to determine a total of 34 cases in the two groups, plus an additional 10% compensate because dry eye metrics often deviate from a normal distribution,[43] plus a 10% dropout rate for withdrawal of consent.

The study population for the efficacy analysis will be the intention-to-treat analysis population, which includes all randomized patients. In addition, a per-protocol set will be defined and analyzed to confirm the robustness of the study results.

The safety analysis will be conducted based on a safety analysis population that includes subjects who have received at least one dose of medication after randomization.

In this study, the level of significance is set at 5% two-sided, and the confidence coefficient is set at 95% unless otherwise specified. The study subject background will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. If the continuous variables clearly do not follow a normal distribution, the variables will be appropriately transformed by logarithmic transformation or other means and aggregated with the mean and standard deviation, or the median and quartile range will be used as descriptive statistics.

For the primary endpoint, between-group comparisons will be performed with baseline as a covariate and an analysis of covariance to calculate the adjusted mean, its 95% confidence interval, and the p-value. Within-group comparisons will be made employing a paired t-test. For safety, frequencies and proportions will be calculated for each group and item, and between-group comparisons will be performed using Fisher's exact probability test or the χ^2 test.

Adverse events

Adverse events are unexpected signs, symptoms, or diseases encountered during the clinical trial, whether or not they are related to the treatment. Local, general, and psychological adverse events may be observed. Local symptoms may include corneal epithelium disorder (filamentary keratitis, superficial keratitis, corneal erosion, etc.), conjunctivitis, eye irritation, eye discharge, conjunctival hyperemia, eye pain, eye itching, ocular foreign body sensation, visual discomfort, hyposphagma, abnormal sensation in the eye (feeling of dry eyes, strange sensation of the eye, sticky eye sensation), blurred vision, photophobia, and lacrimation. If serious adverse events occur, these will be related to the Juntendo Hospital Certified Review Board;

experimental treatments will be stopped immediately, and appropriate treatments will be administered.

Participant withdrawal

Patients will be withdrawn from the study based on the following criteria:

1. When it is judged to be difficult to continue the research due to the occurrence of other diseases.
2. When the study participant becomes untraceable.
3. In the event of pregnancy or suspected pregnancy.
4. When participants or their guardians request to terminate the participation in the research.
5. When the participant's caregiver cannot guarantee cooperation in the research.
6. When the research study itself is discontinued.
7. When the principal investigator and sub-investigators determine that it is appropriate to discontinue the research for other reasons.

Data management

The principal investigator (Takenori Inomata) designated a person (Maria Miura, Juntendo University Faculty of Medicine, Department of Ophthalmology) to be in charge of the data management. This study uses REDCap as a case report form and management tool to collect data. After a database lock, the locked data will be transferred to the person in charge of statistical analysis. Details are specified in the data management manual. After the research is completed, a data management report will be prepared on the implementation and status of the data management, followed by its submission to the principal investigator along with the locked research data.

Limitations

First, the design of this study raises some concerns about confounding effects regarding the postoperative use of three types of eye drops: steroids, antibiotics, and anti-inflammatory drugs. For example, steroid eye drops can improve parameters associated with DED.[44] In addition, three of the postoperative eye drops used in this study contain preservatives. Preservatives may have an adverse effect on postoperative DED.[10, 17, 19] However, all patients in both groups will use the three postoperative eye drops in the same way. Therefore, differences between the two study groups are likely to be caused primarily by the tested eye drops for DED treatment. Second, the study based on this protocol will be a single-blind clinical trial and is not designed as a double-blind study, involving a risk of bias even if the researchers assess the study results as fairly as possible. Third, the sample size of this study is relatively small at 42, and the duration of eye drop implementation is relatively short at 12 weeks. A double-blind study with larger sample size and a longer treatment period could further validate the results of this study.

ETHICS AND DISSEMINATION

Ethics

This study was approved by the Juntendo Hospital Certified Review Board, Tokyo, Japan (approval number: J20-018) and was registered with the Japan Registry of Clinical Trials (jRCT; approval number: jRCT1031210018). Each participant will provide written informed consent prior to participation in the study.

Dissemination plan

The results of the study will be disseminated regardless of the direction of the effect. Trial results will be disseminated to all potential beneficiaries of the study, including patients, caregivers, relatives, physicians, advisory boards, and medical board members. This will take the form of publications in high-impact, open-access medical journals and presentations at national and international medical conferences.

PATIENT AND PUBLIC INVOLVEMENT

There was no direct patient or public involvement in this study.

DATA AVAILAVILITY

All data relevant to the study are included in the article or uploaded as supplementary information.

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MM, TI, YO, KF, KH, YA, MK, and KF will conduct screening and data collection. The analysis will be performed by SN, MN, JS, AKI, MN, and MI.

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Competing interests Dr. Inomata reported receiving grants from Johnson & Johnson Vision Care, Inc., Hogy Medical Co, Ltd., SEED Co, Ltd., Santen Pharmaceutical Co, Ltd., Alcon Japan Ltd., Lion Ltd., and InnoJin Co, Ltd. and personal fees from Santen Pharmaceutical Co, Ltd., outside the submitted work. Dr. Murakami reported receiving grants from Eisai Co, Ltd., Kowa Ltd., Novartis Pharma K.K., HOYA Corporation, ROHTO Pharmaceutical Co, Ltd., Alcon Japan Ltd., AMO Japan K.K., Otsuka Pharmaceutical Co, Ltd., SEED Co, Ltd., Senju Pharmaceutical Co, Ltd., Novartis Pharma K.K., Pfizer Japan Inc, and Santen Pharmaceutical Co, Ltd. and personal fees from Johnson & Johnson Vision Care, Kowa Ltd., and Lion Ltd., outside the submitted work. No other disclosures were reported.

FIGURE LEGEND

Figure 1 Study schema.

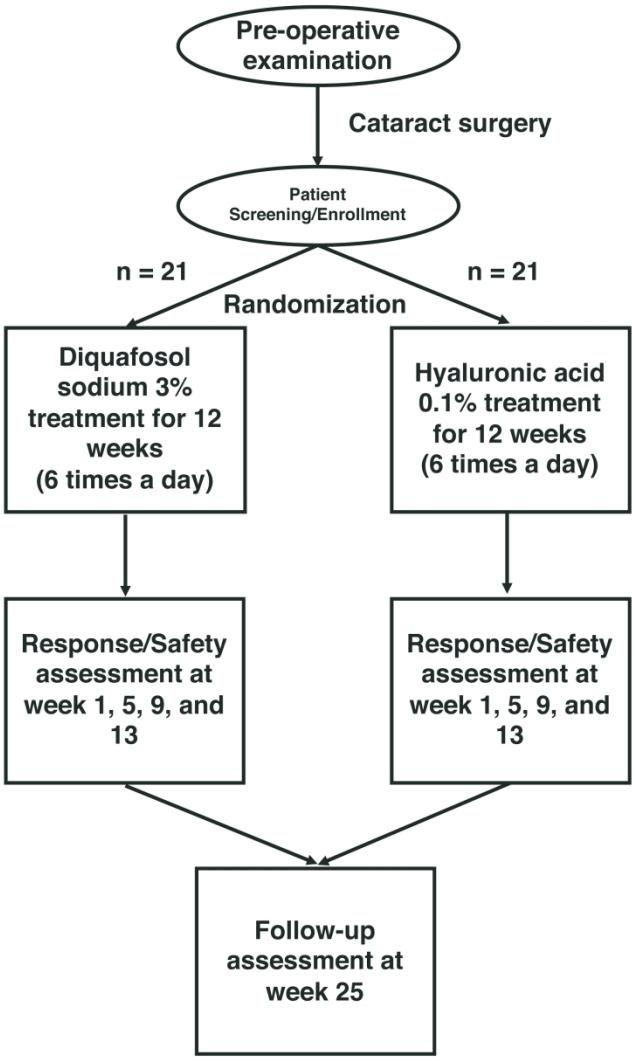
Pre-operative examination
Cataract surgery
Patient Screening/Enrollment
n = 21
n = 21
Randomization
Diquafosol sodium 3% treatment for 12 weeks (6 times a day)
Hyaluronic acid 0.1% treatment for 12 weeks (6 times a day)
Response/Safety assessment at week 1, 5, 9, and 13
Response/Safety assessment at week 1, 5, 9, and 13
Follow-up assessment at week 25

Figure 1

白内障術後ドライアイに対する 3%ジクアホソルとヒアルロン酸 0.1%点眼の効果比較： 単施設ランダム化比較試験

研究計画書

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２０２１年３月３１日　Ver.7.0 作成

更新・承認履歴一覧

日付	Ver.	理由・備考	順天堂医院臨床研究審査委員会承認日
2020年12月25日	1.0	新規作成	年　月　日
2020年11月14日	2.0	提出時コメント反映	
2020年12月26日	3.0	事前コメント反映	
2021年1月15日	4.0	委員会の指示事項の反映	
2021年1月25日	5.0	事前コメント反映	
2021年2月15日	6.0	委員会の指示事項の反映	2021年3月2日
2021年3月31日	7.0	課題名誤記修正	

略語および用語説明

略語および用語	説明
EDC	Electronic Data Capture
OTC	Over the counter
VDT	Visual Display Terminals
DEQS	Dry Eye-related Quality of life Score
OSDI	Ocular Surface Disease Index
J-OSDI	Japanese version of Ocular Surface Disease Index

研究概要

研究の目的		本研究では、白内障手術後における、ステロイド点眼を含む術後の標準的治療の上乗せ治療として、3%ジクアホソルとヒアルロン酸0.1%点眼の有効性の比較を行い、白内障手術期におけるドライアイ加療のエビデンスを創出することを目的とする。	
試験のフェーズ		第Ⅳ相	
Phase		Phase Ⅳ trial	
実施期間		jRCT公開日～2025年11月30日	
実施予定研究対象者数		各群21名の2群合計42名	
試験の種類		介入研究	
Study Type		Interventional Study	
試験デザイン		無作為比較、単盲検、実薬対照、並行群間比較、治療	
Study Design		randomized controlled trial, single blind, active control, parallel assignment, treatment purpose	
プラセボの有無		□ あり	■ なし
盲検の有無		■ あり	□ なし
無作為化の有無		■ あり	□ なし
保険外併用療養の有無		□ あり	■ なし
臨床研究を実施する国(日本以外)		該当なし	
Countries of Recruitment		N/A	
研究対象者の適格基準 Key Inclusion & Exclusion Criteria	主たる選択基準	1) 20歳以上の女性 2) 1眼目の片眼白内障手術より14日以内に両眼の白内障手術を完了した患者 3) 白内障術後ドライアイと診断された患者（Japanese version of Ocular Surface Disease Index（J-OSDI）13点以上かつ涙液層破壊時間5秒以下） 4) 本研究の参加に関して同意（必要に応じて立会人からの同意取得も可能）が文書で得られている患者 5)研究対象者自身で点眼の管理が困難な場合は、本研究に協力できる介護者がいること	
	Inclusion Criteria	(1) Women over 20 years old (2) Patients who have completed cataract surgery in both eyes within 14 days of the first eye cataract surgery in one eye (3) Patients diagnosed with dry eye after cataract surgery (J-OSDI of 13 points or more and tear film breakup time of 5 seconds or less) (4) Patients with written consent (consent can be obtained from a witness if necessary) to participate in this study. (5) If the research subject has difficulty managing the eye drops on his or her own, a caregiver must be available to help with this study.	
	主たる除外基準	1) 白内障術前にドライアイと診断された患者（J-OSDI 13 点以上かつ涙液層破壊時間 5 秒以下） 2) 活動期の眼感染症患者 3) 春季カタルの患者 4) 再発性角膜びらんの患者 5) 遺伝性角膜疾患の患者 6) 睫毛や弛緩した眼球結膜により角膜および結膜に物理的刺激を及ぼしている患者 7) スクリーニング開始時検査から研究薬点眼終了時まで併用制限薬以外の点眼薬（処方薬，OTC 薬をすべて含む）を中止できない患者，使用が予期される患者 8) スクリーニング開始時検査から研究薬点眼終了時までコンタクトレンズの使用を中止できない患者	

		9) 角膜屈折矯正手術術後の患者 10) 涙点プラグを挿入している患者もしくは外科的涙点閉鎖術の既往のある患者 11) 本研究薬の成分及び本研究の検査薬に対する過敏症のある患者 12) その他、研究責任医師が研究対象者として不適当と判断した患者
	Exclusion Criteria	1) Patients with dry eye diagnosed prior to cataract surgery (J-OSDI of 13 points or higher and tear layer breakup time of 5 seconds or less) 2) Patients with active eye infections 3) Spring catarrh patients 4) Patients with recurrent corneal erosions 5) Patients with hereditary corneal disease 6) Patients with physical irritation of the cornea and conjunctiva due to wear and tear or laxity of the ocular conjunctiva. 7) Patients who cannot or will not be able to discontinue ophthalmic medications other than concomitantly restricted medications (including all prescription and OTC medications) from the initial screening examination to the end of the study medication eye drop. 8) Patients who cannot stop using their contact lenses from the start of the screening examination until the end of the study drug eye drop 9) Patients after corneal refractive surgery 10) Patients with a teardrop plug or a history of surgical teardrop closure 11) Patients with hypersensitivity to the components of the study drug and the study's test product 12) Other patients who are deemed by the principal investigator to be unsuitable as research subjects
	年齢下限	20歳以上
	Age Minimum	More than 20 years old
	年齢上限	なし
	Age Maximum	N/A
	性別	女性
	Gender	Female
中止基準		研究対象者ごとの中止基準 1) 疾病等の発現のため、研究の継続が困難と判断された場合 2) 研究対象者が追跡不能となった場合 3) 妊娠または妊娠の疑いが生じた場合 4) 研究対象者及び代諾者からの研究参加取りやめの申し出があった場合 5) 研究に協力出来る介護者がいなくなった場合 6) 本研究自体が中止された場合 7) その他の理由により、研究責任者および研究分担者が研究の中止が適当と判断した場合 研究全体の中止基準 1) 認定臨床研究審査委員会が研究を継続すべきでないと判断した場合 2) 研究の安全性に疑義が生じた場合

	3) 研究の倫理的妥当性や科学的妥当性を損なう事実や情報が得られた場合 4) 研究の実施の適正性や結果の信頼を損なう情報や事実が得られた場合
対象疾患名	白内障術後ドライアイ
Health Condition(s) or Problem(s) Studied	Dry eye disease after cataract surgery
対象疾患キーワード	白内障術後ドライアイ
Keyword	Dry eye disease post cataract surgery
介入の有無	■ あり　□ なし
介入の内容	角結膜上皮障害治療点眼(1.ヒアレイン点眼液0.1%1日6回、2.ジクアス点眼3%1日6回)
Intervention(s)	Hyalein ophthalmic solution, DIQUAS ophthalmic solution 3%
介入キーワード	白内障術後、ドライアイ、自覚症状、
Keyword	Post-cataract surgery, dry eye, subjective symptom
主たる評価項目	投与4週時におけるJ-OSDI（ドライアイ疾患特異的質問紙票)によるJ-OSDI total scoreの絶対値
Primary Outcome(s)	Absolute value of the J-OSDI total score (Dry Eye Disease Specific Questionnaire) at 4 weeks of treatment
副次的な評価項目	・涙液分泌量(シルマー試験)：投与4週時等 ・涙液層破壊時間：投与4週時等 ・フルオレセイン染色スコアー：投与4週時等 ・最大開瞼時間：投与4週時等 ・マイボーム腺機能：投与4週時等 ・J-OSDI(ドライアイ疾患特異的質問紙票)によるJ-OSDI total score（ベースライン、投与8週、投与12週、術後25週） ・涙液分泌量(シルマー試験)（ベースライン、各評価時点） ・涙液層破壊時間（ベースライン、各評価時点） ・フルオレセイン染色スコアー（ベースライン、各評価時点） ・最大開瞼時間（ベースライン、各評価時点） ・マイボーム腺機能（ベースライン、各評価時点） および各項目のベースラインから各評価時点の変化量 また、25週時点のドライアイの再発評価として、ドライアイ診断基準※に該当するかどうかを評価する。 ※涙液層破壊時間5秒以下かつ自覚症状（眼不快感または視機能異常）を有する
Secondary Outcome(s)	Lacrimal secretion (Schirmer test): 4 weeks after administration, etc. Breakage time of the tear film layer: 4 weeks after administration, etc. Fluorescein staining score: at 4 weeks of treatment, etc. Maximum eyelid opening time: 4 weeks of administration, etc. Meibomian gland function: at 4 weeks of treatment, etc. OSDI total score (baseline, 8 weeks of treatment, 12 weeks of treatment, 25 weeks of treatment) based on the J-OSDI (dry eye disease-specific questionnaire) The amount of tear secretion (Schirmer's test) (baseline and at each evaluation point) Breakdown time (baseline and at each evaluation point) Fluorescein staining score (baseline, at each evaluation point) Maximum eyelid opening time (baseline, at each evaluation point) Meibomian gland function (baseline and at each assessment point) and the change at each assessment point from the baseline for each item We will also evaluate whether the patient meets the dry eye diagnostic criteria* for dry eye recurrence at 25 weeks.

	Subjective symptoms (ocular discomfort or visual function abnormalities)

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■ 臨床研究に関連する臨床検査施設、医学的及び技術的部門・機関
該当なし

■ 開発業務受託機関
該当なし

2. 臨床研究の背景

ドライアイは本邦で 2,000 万人以上が罹患する最も多い眼科疾患の一つであり、今後も超高齢化社会、デジタル作業の増加により、ドライアイの増加が懸念されている。[1]ドライアイを発症すると、眼不快感、視力低下などの様々な症状により、視機能の質(QOV)の低下ならびに集中力や生産性の低下から経済的損失の増加が明らかになっている。[2, 3]

白内障手術は最も多い眼科手術であり、高齢化社会により今後も増加することが予想されている。[4]白内障手術は、一般的に安全性で再現性の高い手術として認識されている。そのため、術後の QOV への患者要求が高い。最近の研究から、白内障手術はドライアイ症状を発症・重症化することが明らかになりつつある。

3%ジクアホソルとヒアルロン酸 0.1%点眼はともに、白内障術後のドライアイ治療薬として多く臨床で使われており[5]、ドライアイ治療においては代表的な薬剤でありながら、作用機序は異なっている。ヒアルロン酸 0.1%点眼は、N-アセチル-D-グルコサミンとナトリウム-D-グルコサミンの繰り返し二糖単位からなる天然に存在する線状生体高分子であるヒアルロン酸により、眼表面からの涙液分泌を抑制し、また摩擦を減少させることで主観的症状を軽減する。[6]　それと比較し、P2Y2 受容体の活性化因子である 3%ジクアホソルは、結膜組織からのムチン分泌と涙液分泌を促進し、これにより、角膜および結膜の上皮障害を改善する。[7]

現状ではどちらを選択するかは各々の医師の裁量に委ねられており、明確なガイドラインが存在しないため、白内障術後ドライアイに対する治療方法は未だ定まっていない。

3. 臨床研究の目的

本研究では、白内障手術後における、ステロイド点眼を含む術後の標準的治療の上乗せ治療として、3%ジクアホソルとヒアルロン酸0.1%点眼の有効性の比較を行い、白内障手術期におけるドライアイ加療のエビデンスを創出することを目的とする。

4. 対象疾患

4.1. 対象疾患

白内障術後ドライアイ

4.2. 対象疾患の判断基準

白内障術後にドライアイ診断基準※に該当する患者

※涙液層破壊時間5秒以下かつ自覚症状（眼不快感または視機能異常）を有する

5 臨床研究の方法

5.1 臨床研究デザイン

無作為比較、単盲検、実薬対照、並行群間比較、治療

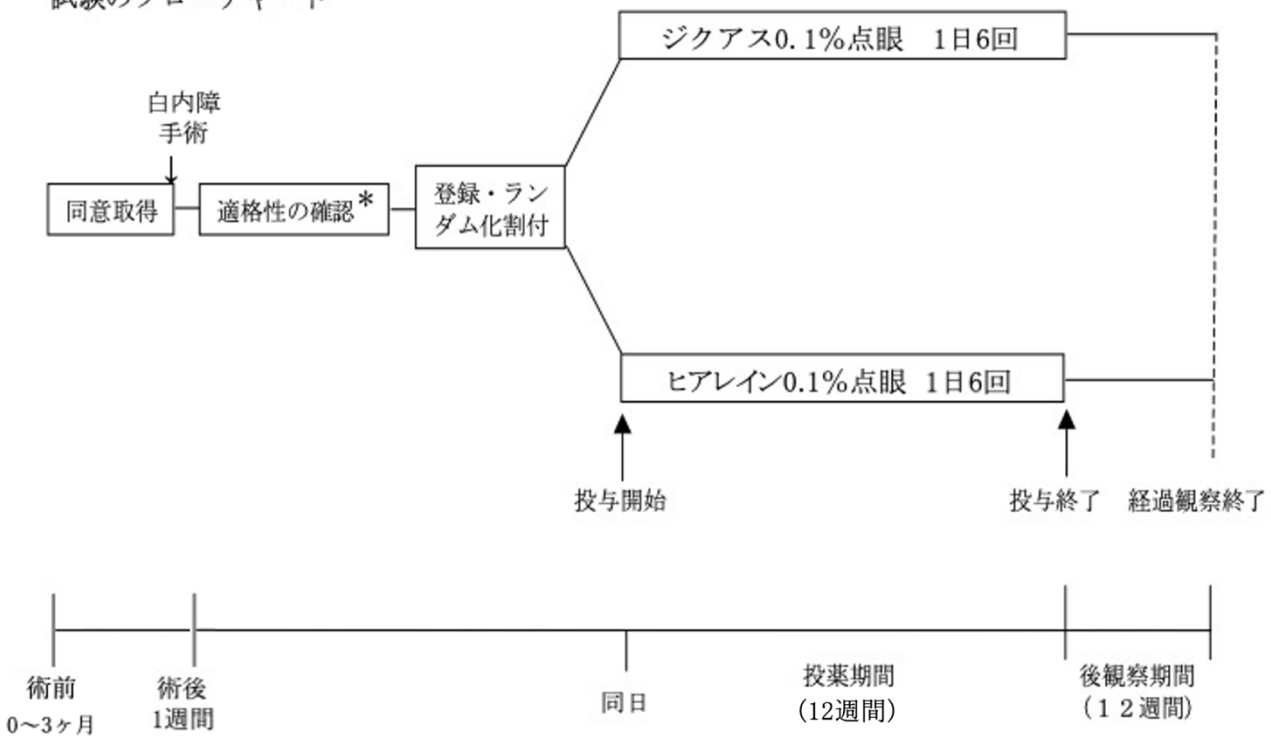
5.2 臨床研究実施期間

研究実施期間 ：jRCT公表日～2025年11月30日

症例登録期間 ：jRCT公表日～2022年12月31日

5.3 臨床研究のアウトライン

試験のフローチャート



6. 臨床研究の対象者の選択基準及び除外基準

下記の選択基準を全て満たし、かつ除外基準のいずれにも該当しない研究対象者を対象とする。

6.1 選択基準

1) 20 歳以上の女性(患者の判断状況や健康状態を医師が判断する)
2) １眼目の片眼白内障手術より 14 日以内に両眼の白内障手術を完了した患者
3) 白内障術後ドライアイと診断された患者（Japanease version of Ocular Surface Disease Index（J-OSDI）13 点以上かつ涙液層破壊時間 5 秒以下）
4) 本研究の参加に関して同意（必要に応じて代諾者からの同意取得も可能）が文書で得られている患者
5) 研究対象者自身で点眼の管理が困難な場合は、本研究に協力できる介護者がいること

[設定根拠]

1) ドライアイは疫学的に性別(女性)がリスク因子となるため今回の対象は女性のみに限定した
2) Outcome 指標である自覚症状に片眼、両眼の手術が影響を与えるため、両眼白内障手術を受けた患者に限定した
3) Asia Dry Eye Society による 2016 年ドライアイ診断基準による。
4) 同意取得を得ることは倫理通念上必要不可欠である。
5) 研究遂行のため点眼管理が不可欠である。

6.2 除外基準

1)白内障術前にドライアイと診断された患者（J-OSDI 13 点以上かつ涙液層破壊時間 5 秒以下）
2)活動期の眼感染症患者
3)春季カタルの患者
4)再発性角膜びらんの患者
5)遺伝性角膜疾患の患者
6)消耗や弛緩した眼球結膜により角膜および結膜に物理的案刺激を及ぼしている患者
7)スクリーニング開始時検査から研究薬点眼終了時まで併用制限薬以外の点眼薬（処方薬，OTC 薬をすべて含む）を中止できない患者，使用が予期される患者
8)スクリーニング開始時検査から研究薬点眼終了時までコンタクトレンズの使用を中止できない患者
9)角膜屈折矯正手術術後の患者
10)涙点プラグを挿入している患者もしくは外科的涙点閉鎖術の既往のある患者
11)本研究薬の成分及び本研究の検査薬に対する過敏症のある患者
12) 緑内障点眼を使用している患者
13)その他、研究責任医師が研究対象者として不適当と判断した患者

[設定根拠]

1) 研究を実施しても結果の評価が不可能である。
2) リスクが高くなり臨床研究に組み入れることが倫理的でない。
3) リスクが高くなり臨床研究に組み入れることが倫理的でない。
4) リスクが高くなり臨床研究に組み入れることが倫理的でない。
5) 研究を実施しても結果の評価が不可能である。
6) 研究を実施しても結果の評価が不可能である。
7) 研究を実施しても結果の評価が不可能である。
8) 研究を実施しても結果の評価が不可能である。

9) 研究を実施しても結果の評価が不可能である。
10) 研究を実施しても結果の評価が不可能である。
11) リスクが高くなり臨床研究に組み入れることが倫理的でない。
12) 研究を実施しても結果の評価が不可能である。
13) 研究を実施しても結果の評価が不可能である。

7 研究対象者の登録方法・割付方法

7.1 登録方法

1) 研究責任医師または研究分担医師は、選択基準及び除外基準に基づいた適合条件に合致している者から、被験者の自由意思に基づく文書同意を得る。必要に応じて立会人から同意を取得する。

2) 研究責任医師または研究分担医師は、登録適格性確認票に必要事項をすべて記入する。登録適格性確認票は各施設で適切に保管する。

7.2 割付方法

本研究では割付け責任者が作成した割付表に従って割付けを行う。適格性を確認した被験者について、層別置換ブロック法にて 0.1%ヒアレイン酸点眼剤群、ジクアス 3%点眼剤群に、１：１にランダムに割り付ける。割付因子は年齢 80 歳未満・以上とする。

7.3 盲検化

単盲検とする。

8 研究の中止基準

8.1 研究対象者ごとの中止基準

研究責任医師、研究分担医師は、以下のような研究対象者の医学的状態の変化により当該研究対象者がこれ以上安全に臨床研究に参加することが出来ないと判断した場合、また、研究対象者及び代諾者からの研究参加取りやめの申し出があった場合は、研究期間のいかなる時期であっても研究対象者の参加を中止しなければならない。

1） 疾病等の発現のため、研究の継続が困難と判断された場合
2） 研究対象者が追跡不能となった場合
3） 妊娠または妊娠の疑いが生じた場合
4） 研究対象者及び代諾者からの研究参加取りやめの申し出があった場合
5） 研究に協力出来る介護者がいなくなった場合
6） 本研究自体が中止された場合
7） その他の理由により、研究責任者および研究分担者が研究の中止が適当と判断した場合

8.2 臨床研究全体の中止基準

下記に該当した場合は研究全体を中止する。研究責任医師は、研究を中止した場合には、研究対象者に中止したことを速やかに通知し、適切な医療の提供やその他の必要な措置を講ずる。研究責任医師は、研究を中止したときには、中止及びその理由、結果概要を文書により遅滞なく病院長に報告する。

1） 認定臨床研究審査委員会が研究を継続すべきでないと判断した場合
2） 研究の安全性に疑義が生じた場合
3） 研究の倫理的妥当性や科学的妥当性を損なう事実や情報が得られた場合
4） 研究の実施の適正性や結果の信頼を損なう情報や事実が得られた場合

9　臨床研究の対象者に対する治療/介入

9.1 臨床研究に用いる医薬品等の概要

1）ジクアホソルナトリウム

販　売　名　　：ジクアス点眼 3%（一般名：ジクアホソルナトリウム）
性状・剤形　　：点眼剤
含　　量　　：1mL 中ジクアホソルナトリウム 30mg 含有
貯　　法　　：室温保存
製　造　元　　：参天製薬株式会社
承認効能　　：ドライアイ
用法・用量　　：通常、1 回 1 滴、1 日 6 回点眼する。
主な副作用：詳細は添付文書参照

2）精製ヒアルロン酸ナトリウム

販　売名　　：ヒアレイン点眼液 0.1%（一般名：精製ヒアルロン酸ナトリウム）
性状・剤形　　：点眼剤
含　　量　　：1mL 中精製ヒアルロン酸ナトリウム 1mg 含有
貯　　法　　：室温保存
製　造　元　　：参天製薬株式会社
承認効能　：（添付文書より抜粋）下記疾患に伴う角結膜上皮障害
・シェーグレン症候群、スティーブンス・ジョンソン症候群、眼球乾燥症候群（ドライアイ）等の内因性疾患
・術後、薬剤性、外相、コンタクトレンズ装用等による外因性疾患
用法・用量　　：1 回 1 滴、1 日 5～6 回点眼し、症状により適宜増減する。
主な副作用：詳細は添付文書参照

10　投薬・手術・検査等の介入を行う手順

10.1　投薬部位・手術部位・検査部位等

点眼投与：基本目安時間を 7 時、10 時、13 時、16 時、19 時、22 時と定め、ライフスタイルに合わせ、1、2 時間程度の時間の前後は可とする。ルーチン点眼と同じタイミングでする場合は、全てのルーチン点眼の最後に、直前の点眼から 5 分以上空けて使用することとし、また、患者説明同意書に、被験者負担が増えることを明記する。
また、試験以外の介入は以下の通り統一する。術式は強角膜切開、切開幅 2.4㎜ とする。
術後ルーチン点眼は術後 1 ヶ月まではガチフロ（ガチフロキサシン）0.3%点眼 1 日４回、サンベタゾン（ベタメタゾンリン酸エステルナトリウム）0.1%点眼 1 日４回、ブロナック（ブロムフェナクナトリウム）0.1%点眼 1 日２回、それ以降術後 3 ヶ月まではガチフロ 0.3%点眼 1 日４回、フルメトロン（フルオロメトロン）0.1%点眼 1 日４回、ブロナック 0.1%点眼 1 日２回とする。

10.2　投薬・手術・検査等の介入を行う時期・期間

治療介入期間
本登録後、12 週間、治療介入期間用試験薬を点眼する。さらに術後 14 週から 25 週の後観察期間 12 週間で、点眼薬の持続効果や、ドライアイの再発を確認する。

10.3　用法・用量、回数、所要時間等

ジクアス点眼3% 1日6回、精製ヒアルロン酸ナトリウム1日6回点眼する。

10.4　増量・減量の目安等

薬剤投与により下記症状が発現し、また薬剤投与との関連が強く疑われる場合、医師の判断により休薬を実施する。

＜薬剤＞ジクアス点眼 3%
＜症状＞
眼脂、結膜充血、眼痛、掻痒感、異物感、不快感、結膜下出血、眼の異常感、霧視、羞明、流涙、刺激感、角膜上皮障害、結膜炎

＜薬剤＞ヒアレイン点眼液 0.1%
＜症状＞
眼瞼掻痒感、眼刺激感、結膜充血、眼瞼炎

11　併用薬及び併用療法

11.1　併用禁止薬及び禁止療法

下記の白内障術後にルーチンで行う点眼薬以外の点眼薬

11.2　併用可能薬・可能療法

白内障術後点眼薬として
・ガチフロ点眼液 0.3%（術翌日～12 週）
・ブロナック点眼液 0.1%（術翌日～12 週）
・サンベタゾン眼耳鼻科用液 0.1%（術翌日～4 週）
・フルメトロン点眼液 0.1%（5 週～12 週）
を使用する。

12. 観察・検査項目及び実施時期，データ収集の方法

12.1.　観察・検査スケジュール

期間	前観察期		投与期（12 週間）				後観察期間（１２週）
項　目	白内障術前	白内障手術	白内障術後				
時　期	0～3 ヶ月前	0 週	術後 1 週後（投与０日）	術後 5 週後（投与 4 週）	術後 9 週後（投与 8 週）	術後 13 週後（投与 12 週）	術後 25 週後
許容範囲	－	－	±2 日	±7 日	±7 日	±7 日	±7 日
受　診	受診 1	受診 2	受診 3	受診 4	受診 5	受診 6	受診 7
同意取得	○						
本登録			○				
研究対象者背景の確認	○						
白内障術後点眼薬		○ ←	—	—	—	→	
試験薬投与			←	—	—	→	
質問紙票回答	○		○	○	○	○	○

有害事象の観察[a]			←				→
生活習慣情報	○		○	○	○	○	○
白内障術前後検査	○		○	○	○	○	○
白内障手術情報		○					
ドライアイ検査	○		○	○	○	○	○
患者日誌		○	←				→

12.2. 観察・検査項目

○対象者背景等: 年齢、性別、診断名、高血圧の有無、糖尿病の有無、膠原病の有無、コンタクトレンズ使用歴、眼圧上昇の既往、眼手術の既往、角膜疾患の既往、精神疾患の既往、花粉症の有無

○生活習慣情報の問診: 頭痛、肩こり、VDT 時間、睡眠時間、運動の頻度と種目、睡眠薬内服の有無、喫煙の有無等の生活習慣情報

○白内障術前後検査: 矯正視力、眼圧、コントラスト感度、角膜曲率半径、角膜内皮細胞密度、細隙灯検査、眼底検査

○手術情報: 術式、手術時間、合併症、執刀医情報

○ドライアイ検査: 自覚症状スコアー(J-OSDI 質問紙票)、涙液分泌量(シルマー試験)、涙液層破壊時間、フルオレセイン染色スコアー、最大開瞼時間、マイボーム腺機能

○有害事象 (眼刺激感、眼脂、結膜充血、眼痛、眼そう痒感、眼不快感、流涙、眼瞼炎、過敏症、眼異物感を含む)

○患者日誌: 日時、点眼回数、点眼できなかった理由、眼や体調の変化、薬の使用記録

12.3 観察・検査方法

以下の順に観察・検査を行う

①問診票による自覚症状スコアー(J-OSDI 質問紙票)

②診察、生活習慣情報の問診:を医師による対面で実施する

③白内障術後検査(矯正視力、眼圧、コントラスト感度、角膜曲率半径、角膜内皮細胞密度):眼科検査室で実施する

④細隙灯検査ならびに眼底検査を医師対面で実施する。

⑤ドライアイ検査(涙液層破壊時間、フルオレセイン染色スコアー、最大開瞼時間、マイボーム腺機能)を医師が対面に実施する

⑥涙液分泌量(シルマー試験)を看護師が検査室で実施する

13. 評価項目

13.1. 有効性評価項目

13.1.1. 主要評価項目 (プライマリーエンドポイント)

投与 4 週時の J-OSDI (ドライアイ疾患特異的質問紙票)による J-OSDI total score の絶対値

13.1.2. 副次的評価項目 (セカンダリーエンドポイント)

・涙液分泌量(シルマー試験):投与 4 週時等

・涙液層破壊時間:投与 4 週時等

・フルオレセイン染色スコアー:投与 4 週時等

・最大開瞼時間:投与 4 週時等

・マイボーム腺機能:投与 4 週時等

・J-OSDI（ドライアイ疾患特異的質問紙票)による J-OSDI total score（ベースライン、投与8週、投与１２週、術後２５週）
・涙液分泌量(シルマー試験)（ベースライン、各評価時点）
・涙液層破壊時間（ベースライン、各評価時点）
・フルオレセイン染色スコアー（ベースライン、各評価時点）
・最大開瞼時間（ベースライン、各評価時点）
・マイボーム腺機能（ベースライン、各評価時点）
および各項目のベースラインから各評価時点の変化量

また、２５週時点のドライアイの再発評価として、ドライアイ診断基準※に該当するかどうかを評価する。
※涙液層破壊時間 5 秒以下かつ自覚症状（眼不快感または視機能異常）を有する

13.2 安全性評価項目
有害事象、視力、眼圧、薬剤性アレルギーの有無、細隙灯顕微鏡による評価(結膜充血、眼瞼炎の有無)

14. 疾病等発生時の取り扱い
本研究は介入研究であり，日常診療に加えて、研究対象者の試料・情報を利用するものである。その際，試料・情報の採取に侵襲性を有するため，研究対象者に健康被害が発生する可能性がある。その際は，研究責任医師は誠意を持って対処し，適切な医療を提供する。その費用は研究対象者の保険診療で行い、本研究による特別の補償は行わない。以上の点をあらかじめ研究対象者に説明し，同意を得ることとする。

14.1 疾病等
ジクアス点眼 3%、精製ヒアルロン酸ナトリウムの添付文書参照。
14.1.1 疾病等の定義
疾病等とは、臨床研究の実施に起因するものと疑われる疾病、障害若しくは死亡または感染症に加え、臨床検査値の異常や諸症状を含むものをいう。

14.2 予測される疾病等
ジクアス点眼 3%: 眼脂、結膜充血、眼痛、掻痒感、異物感、不快感、結膜下出血、眼の異常感、霧視、羞明、流涙、刺激感、角膜上皮障害、結膜炎

ヒアレイン点眼液 0.1%: 眼瞼掻痒感、眼刺激感、結膜充血、眼瞼炎

14.3 予測できない疾病等
「14.2.予測される疾病等」の項で指定された以外の疾病等。

14.4 重篤度の判断
疾病等のうち、次のいずれかに該当するものとするものは、重篤な疾病等とする。
(1) 死亡
(2) 死亡につながるおそれのある疾病等
(3) 治療のために医療機関への入院又は入院期間の延長が必要とされる疾病等
(4) 障害

(5) 障害につながるおそれのある疾病等
(6) (3)～(5)まで並びに死亡及び死亡につながるおそれのある疾病等に準じて重篤である疾病等
(7) 後世代における先天性の疾病又は異常

14.5 重篤な疾病等発生時の研究対象者への対応

研究責任医師は、疾病等を認めた場合には、直ちに適切な処置を行う。
なお、本研究は保険診療内で行われるため、研究対象者に健康被害が発生した場合であっても、その費用は研究対象者の保険診療で行い、本研究による特別の補償は行わない。以上の点をあらかじめ研究対象者に説明し，同意を得ることとする。

14.6 疾病等の報告

研究責任医師は、本研究の実施において疾病等の発生を知った場合には、速やかに、その旨を実施医療機関の管理者に報告した上で、認定臨床研究審査委員会へ報告する。
認定臨床研究審査委員会が疾病等の報告に対し、意見を述べた時は、研究責任医師は、当該意見を尊重して必要な措置をとる。
なお、実施医療機関の管理者及び認定臨床研究審査委員会への報告は、以下の期間内に行う。

①死亡（感染症によるものを除く）の発生のうち、承認内の医薬品等を用いる特定臨床研究の実施によるものと疑われるもの 15 日
②以下の疾病等（感染症を除く）の発生のうち、承認内の医薬品等を用いる特定臨床研究の実施によるものと疑われるものであって、かつ、当該特定臨床研究に用いた医薬品等の添付文書または容器若しくは被包に記載された使用上の注意（以下「使用上の注意等」という。）から予測することができないものまたは当該医薬品等の使用上の注意等から予測することができるものであって、その発生傾向を予測することができないもの若しくはその発生傾向の変化が保健衛生上の危害の発生若しくは拡大のおそれを示すもの 15 日
(a) 治療のために医療機関への入院または入院期間の延長が必要とされる疾病等
(b) 障害
(c) 死亡又は障害につながるおそれのある疾病等
(d) 死亡又は（a）から（c）までに掲げる疾病等に準じて重篤である疾病等
(e) 後世代における先天性の疾病または異常
③承認内の医薬品等を用いる特定臨床研究の実施によるものと疑われる感染症による疾病等の発生のうち、当該医薬品等の使用上の注意等から予測することができないもの 15 日
④承認内の医薬品等を用いる特定臨床研究の実施によるものと疑われる感染症による死亡または②（a）から（e）までに掲げる疾病等の発生（③にかかるものを除く。） 15 日
⑤②（a）から（e）までの疾病等の発生のうち、当該特定臨床研究の実施によるものと疑われるもの（②に掲げるものを除く。） 30 日
⑥上記①～⑤以外については、定期報告（実施計画を提出した日から起算して、1 年ごとに、当該期間満了後 2 か月以内）の際に行う。

14.7 救済処置

14.7.1 救済薬の交付、治療方法

試験薬を中止し、医師の判断の元、適切な処置を行う。

14.7.2 急性増悪等緊急時の処置

試験薬を中止し、医師の判断の元、適切な処置を行う。

15　統計学的事項

15.1　　目標症例数および設定根拠

目標症例数　42 例

平均の差に対する t 検定(検出力 0.8, 有意水準 5%, 臨床的に有効とされる差　自覚症状スコア 5.24 [5], 比較群の標準偏差 5.23 [5]により、2 群合計 34 例になり、ドライアイのデータの特徴により 10%上乗せし[8]、さらに同意撤回脱落を 10%と設定し、42 例を目標症例数とする。

15.2　　解析対象集団

本試験の有効性解析対象集団は、ランダム化されたすべての症例を対象とした、Intention-to-treat(ITT)解析対象集団とする。また、試験結果の頑健性を確認するために、試験実施計画書に適合した対象集団（per-protocol set: PPS）も定義し、解析を実施する。

安全性については、ランダム化後に一度でも投薬された研究対象者を含む対象集団を、安全性解析対象集団として、解析を実施する。

15.3　　集計・解析方法

本試験では、特に定める場合を除いて有意水準を両側 5%、信頼係数を 95%とする。

研究対象者背景は、連続変数は平均値及び標準偏差、カテゴリカル変数に関しては、頻度と割合を算出して集計する。連続変数が明らかに正規分布に従わない場合は、変数を対数変換などで適切に変換し、平均値および標準偏差で集計するか、または、中央値、四分位範囲を記述統計量として使用する。

主要評価項目について、群間比較はベースラインを共変量とした、共分散分析を行い、調整された平均値、その 95%信頼区間、p 値を算出する。また、経時データ解析を行う。

安全性については、群ごと、項目ごとに頻度と割合を算出し、フィッシャーの正確確率検定あるいは χ^2 検定で群間比較を実施する。

探索的な解析・ビジュアル化に関する解析を実施する。

15.4　　欠落、不採用及び異常データの取扱いの手順

欠測値の補完はしない。

15.5　　当初の統計的な解析計画を変更する場合の手順

当初の統計的な解析計画からの変更がある場合は、研究計画書又は統計解析計画書を改訂し、臨床研究の総括報告書に記載する。

15.6　　中間解析と研究の早期中止

本試験では中間解析を実施しない。

15.7.その他、探索的解析

主要評価項目に影響を与えると考えられるベースラインの因子が、群間で異なる場合、当該因子を共変量とした共分散分析を実施する。

16. 原資料等の閲覧

研究責任医師及び実施医療機関は、臨床研究に関連するモニタリング、監査並びに認定臨床研究審査委員会及び規制当局による調査の際に、原資料等すべての臨床研究関連記録を直接閲覧に供する。

17. 品質管理及び品質保証

17.1 モニタリング及び監査

17.1.1 モニタリング

実施体制

本研究のモニタリングは、研究責任医師がモニター指定書により指定した
順天堂大学医学部附属順天堂医院　臨床研究・治験センターに所属する者が実施する。

連絡先：〒113-8431　東京都文京区本郷 3-1-3
TEL(直通) 03-3814-5672　(内線)3832

モニタリングの方法

本研究のモニタリングは、中央モニタリングにより行う。

○モニタリング対象施設

順天堂大学医学部附属順天堂医院　眼科

モニタリングの実施時期

モニターは、本研究の実施期間中に 1 回モニタリングを実施する。モニターは、モニタリング実施後、報告書を作成し、研究責任医師に提出する。

モニタリング項目

モニターは、以下の項目を確認する。

1) 症例集積達成状況、登録症例数
2) 登録された症例の適格性
登録された症例が研究計画書に規定されている選択基準に合致し、除外基準に該当していないことを確認する。
3) 疾病等の有無、内容
疾病等の発生の有無、発生した疾病等に対して適切に対応されていることを確認する。
4) 不適合の有無、内容
研究計画書、臨床研究法等からの不適合の有無、不適合が発生していた場合は適切に対応されていることを確認する。
5) 中止例の有無、中止の場合はその理由
6) 試験の進捗や安全性に関する問題点
7) その他、研究責任医師が必要とする事項

17.1.2. 監査

実施体制

本研究の監査は、順天堂大学医学部附属順天堂医院　臨床研究・治験センター　臨床研究コンプライアンス・ガバナンス推進室室長の指名により、研究責任医師が監査員指定書をもって指定した者が実施する。

連絡先：〒113-8431　東京都文京区本郷 3-1-3
TEL(直通) 03-3814-5672　(内線)3832

監査の方法

(1) 本研究の監査は、施設訪問監査により行う。

○監査対象施設
順天堂大学医学部附属順天堂医院　眼科
(2) 直接閲覧（SDV）は、実施医療機関の手順等の定めに従って実施する。

監査の実施時期
監査員は、本研究の終了時に監査を実施する。監査員は、監査を実施後１ヶ月以内に監査報告書を作成し、研究責任医師に提出する。

監査項目
監査員は、以下の項目を確認する。
・臨床研究審査委員会の手続き関連書類
・研究対象者より取得した同意書、同意撤回書
・研究対象者識別コードリスト
・個人情報の保管・管理状況
・症例の適格性の確認
・受診、検査の実施状況
・研究中止例数、中止理由
・疾病等の有無、内容、対応状況
・臨床研究法施行規則又は研究計画書からの不適合の内容、対応状況
・モニタリングの実施結果、モニタリング報告書の保管状況
・その他、研究責任医師が必要とする事項

17.2 データマネジメント
本研究では、研究責任医師が指定したデータマネジメント担当者（順天堂大学医学部眼科学教室　三浦真里亜)がデータマネジメントを実施する。CRF 及びマネジメントツールとして REDCap を用いデータ収集を行う。データ固定後に、統計解析責任者に対して固定データが提供される。詳細に関しては、データマネジメントマニュアルに規定する 。研究終了後にはデータマネジメント業務の実施状況についてデータマネジメント報告書を作成し、固定した研究データとともに研究責任医師に提出する。

18. 倫理的な配慮
18.1 遵守すべき諸規則
本研究に携わるすべての者は、人を対象とする全ての医学研究が準拠すべき「世界医師会ヘルシンキ宣言」、「人を対象とする医学系研究に関する倫理指針」及び「臨床研究法」の内容を熟読し理解した上で遵守し、研究を施行する。

18.2 研究対象者の個人情報及びプライバシーの保護
研究に関わる関係者は、研究対象者の個人情報保護について、適用される法令、条例を遵守する。 また関係者は、研究対象者の個人情報及びプライバシー保護に最大限の努力を払い、本研究を行う上で知り得た個人情報を正当な理由なく漏らしてはいけない。関係者がその職を退いた後も同様とする。
本研究は順天堂医院と情報の授受が発生する。提供元の共同研究機関の名称、研究責任医師名、授受の発生した日付、研究対象者名（研究用 ID を含む）、インフォームド・コンセントの有無をデータベースへ記録し、順天堂大学医学部眼科学教室の盗難防止策の施されたコンピューターに保管する。
研究実施に係る個人情報を取扱う際は、各参加施設の(個人情報管理者等)によって、個人情報とは関係ない研究用ＩＤを付して管理し、研究対象者の秘密保護に十分配慮する。作成した対応表は、眼科学研究室の鍵のかかるロッカーで猪俣武範が厳重に管理する。患者個人情報を本

学へ送る際は、研究用ＩＤを使用して、電子的配信等にて本学へ送付される。受領した情報は、本学の眼科研究室の鍵のかかるロッカーで保管され、猪俣武範が厳重に管理する。また、研究の目的以外に、研究で得られた研究対象者の個人情報を使用しない。

19 臨床研究の対象者に対する説明及び同意を得る方法

19.1 研究対象者に生じる負担並びに予測されるリスク及び利益の要約

本研究で用いる薬剤はいずれも本研究の対象に対して適応が承認され保険適用されているものであり、いずれの群の治療法も日常保険診療として行われ得る治療法であることから、研究対象者が本研究に参加することによって生じると予測される直接的な利益はなく、不利益についても同様である。ただし、急速漸減グループに割付けられた研究対象者は標準治療に比して再燃率が上昇する可能性が棄却できないため、再燃に伴う不利益が生じる可能性がある。また、研究対象者は各来院時に、20 分程度の検査診察時間が追加される。

19.2 予測される利益

本研究で用いる薬剤はいずれも本研究の対象に対して適応が承認され保険適用されているものであり、いずれの群の治療法も日常保険診療として行われ得る治療法である。また、研究対象者の研究期間中の薬剤費を含む診療費はすべて患者の保険及び患者自己負担により支払われるため、研究対象者が研究に参加することで得られる、特別な診療上、経済上の利益はない。

19.3 予測される危険と不利益及びそれらを最小化する対策

薬剤による治療は、本研究では日常診療の一環として行われるものである。治療にあたり、疾病等/副作用発現のリスクは生じるが、本研究に参加することにより、日常診療に比べてこれらのリスクが上昇することはない。

19.4 同意を得る手順

研究責任医師、研究分担医師は、研究対象者に対して別に定める説明・同意文書に基づき、本臨床研究に参加する前に研究の内容について十分に説明する。

なお、説明・同意文書は研究責任医師が作成し、認定臨床研究審査委員会の承認を得た後に使用する。改訂する場合は再度認定臨床研究審査委員会に申請し、承認を得た後に使用する。

臨床研究に参加するかどうかについて十分考える時間を与えた後、研究責任医師及び研究分担医師は本人の自由意思による研究参加の同意を文書（別途定める同意文書）で得る。

代諾者は、視力低下等の原因で承諾書への記載が困難な場合、また高齢等で意思能力が不自由な場合に必要となる。

代諾者は、研究対象者の代理人（代理権を付与された任意後見人を含む。）とする。

19.5 同意説明文書の内容

同意文書に記載する項目は以下の通りとする。

1) 臨床研究の名称及び当該臨床研究の実施について研究機関の長の許可を受けている旨及び厚生労働大臣に実施計画を提出している旨
2) 研究機関の名称及び研究責任者の氏名及び職名
（他の研究機関と共同して研究を実施する場合には、研究代表医師の氏名及び職名並びに共同研究機関の名称及び共同研究機関の研究責任者の氏名び職名を含む。）
3) 臨床研究の目的及び意義
4) 臨床研究の方法（研究対象者から取得された試料・情報の利用目的を含む。）及び期間
5) 研究対象者として選定された理由
6) 研究対象者に生じる負担並びに予測されるリスク及び利益
7) 臨床研究が実施又は継続されることに同意した場合であっても随時これを撤回できる旨
（研究対象者等からの撤回の内容に従った措置を講じることが困難となる場合があるとき

は、その旨及びその理由）
8) 臨床研究が実施又は継続されることに同意しないこと又は同意を撤回することによって研究対象者等が不利益な取扱いを受けない旨
9) 臨床研究に関する情報公開の方法
10) 研究対象者又はその代諾者の求めに応じて、他の研究対象者等の個人情報等の保護及び当該研究の独創性の確保に支障がない範囲内で研究計画書及び臨床研究の方法に関する資料を入手又は閲覧できる旨並びにその入手又は閲覧の方法
11) 個人情報等の取扱い（匿名化する場合にはその方法、匿名加工情報又は非識別加工情報を作成する場合にはその旨を含む。）
12) 試料・情報の保管及び廃棄の方法
13) 臨床研究の資金源等、研究機関の研究に係る利益相反及び個人の収益等、研究者等の研究に係る利益相反に関する状況
14) 研究対象者等及びその関係者からの苦情及び問合せへ等への対応
15) 研究対象者等に経済的負担又は謝礼がある場合には、その旨及びその内容
16) 通常の診療を超える医療行為を伴う臨床研究の場合には、他の治療方法等に関する事項
17) 通常の診療を超える医療行為を伴う研究の場合には、研究対象者への研究実施後における医療の提供に関する対応
18) 臨床研究の実施に伴い、研究対象者の健康、子孫に受け継がれ得る遺伝的特徴等に関する重要な知見が得られる可能性がある場合には、研究対象者に係る研究結果（偶発的所見を含む。）の取扱い
19) 侵襲を伴う臨床研究の場合には、当該研究によって生じた健康被害に対する補償の有無及びその内容
20) 研究対象者から取得された試料・情報について、研究対象者等から同意を受ける時点では特定されない将来の研究のために用いられる可能性又は他の研究機関に提供する可能性がある場合には、その旨と同意を受ける時点において想定される内容
21) 侵襲（軽微な侵襲を除く。）を伴う臨床研究であって介入を行うものの場合には、研究対象者の秘密が保全されることを前提として、モニタリングに従事する者及び監査に従事する者並びに認定臨床研究審査委員会が、必要な範囲内において当該研究対象者に関する試料・情報を閲覧する旨

20　記録（データを含む。）の取扱い及び保存

20.1　　他機関への試料・情報の提供の有無

該当なし

20.1.1　他機関への試料・情報の提供の有無

☐　あり

☑　なし

20.1.2　試料・情報の保管及び廃棄の方法

該当なし

20.2　　研究に係る試料及び情報等の保管

研究責任医師は、研究等の実施に係わる文書（申請書類の控え、病院長からの通知文書、各は種申請書・報告書の控、研究対象者識別コードリスト、同意書、症例報告書等の控、その他データの信頼性を保証するのに必要な書類又は記録など）を保存し、研究終了後 5 年間に保存する。

廃棄する場合には、個人が特定できないよう、匿名化したまま廃棄する。

20.3　研究対象者から取得された試料・情報の二次利用について
本研究で得られたデータについては、認定臨床研究審査委員会の審査を経て承認された場合に限り、個人識別情報とリンクしない形で二次利用することがあり得る。

21　研究対象者の健康、子孫に受け継がれ得る遺伝的特徴等に関する重要な知見が得られた場合の研究対象者に係る研究結果（偶発的所見を含む。）の開示について
本研究は、研究対象者の健康、子孫に受け継がれ得る遺伝的特徴等に関する研究ではないため、該当なし。

22　臨床研究の実施に係る金銭の支払及び補償
22.1　保険への加入の有無とその内容
☑　加入する
☐　加入しない

重篤な合併症が起きた場合の補償

22.2　健康被害に対する補償・賠償
研究責任医師は、疾病等を認めた場合には、直ちに適切な処置を行う。
なお、本研究は保険診療内で行われるため、研究対象者に健康被害が発生した場合であっても、その費用は研究対象者の保険診療で行うが、重篤な合併症が起きた場合は、加入した臨床研究保険で補償される。
また、各研究対象者の研究終了後、当該研究の結果により得られた最善の医療（予備、診断及び治療）を受けることができるよう努力する。

22.3　予測される医療費（研究対象者の負担）
本研究で用いる研究薬および実施する検査は保険診療内で行われるため、研究に参加することによる研究対象者の費用負担は発生しない。一般保険診療に該当する負担のみ生じる。

22.4　研究対象者に対する金銭の支払、医療費の補助
本研究では被験者への謝礼は発生しない。本研究で用いる研究薬および実施する検査は保険診療内で行われるため、研究に参加することによる研究対象者の費用負担は発生しない。

23　臨床研究に関する情報の公表
23.1　研究に関する登録
研究に関する情報は、厚生労働省が設置している公開データベース：JRCT（Japan Registry of Clinical Trials、URL: https://jrct.niph.go.jp/）に登録する

23.2　研究に関する情報の更新
JRCT に登録した情報は、適宜、一更新等を行う。

23.3　研究成果の帰属と結果の公表
本研究で得られた結果は、日本眼科学会総会ならびに日本臨床眼科学会で発表し、眼科学領域の専門学術誌で論文として公表する予定である。いずれの場合においても公表する結果は統計的な処理を行ったものだけとし、研究対象者の個人情報は一切公表しない。
研究代表医師は、主要評価項目データの収集期間が終了した日から１年以内に主要評価項目報告書を、全てのデータの収集期間が終了した日から１年以内に総括報告書・総括報告書の概要をそれぞれ作成し、認定臨床研究審査委員会の意見を聴いた日から起算して１月以内に JRCT に公開する。

24　臨床研究の適正な実施のために必要な事項

24.1　　本臨床研究に対する医薬品等製造販売業者等による研究資金の提供等

□　あり

☑　なし

24.2　　研究資金の拠出元

本研究は、学内研究費（令和元年 CORE プロジェクト研究費）で賄われ、特定の企業からの資金は一切用いない。

利益相反の管理については、研究責任（代表）医師が臨床研究法における臨床研究の利益相反管理ガイダンスに従い、利益相反管理基準及び利益相反管理計画を認定臨床研究審査委員会に提出し承認を得ている。

24.3　　利益相反

医局では研究対象薬のヒアレイン、ジクアスを販売している参天製薬からの奨学寄付金、研究責任医師の主催事業であるアレルサーチの公式 HP 作成に対し寄附金(申告基準未満)を受領しているが、本研究ではそれらの寄附金は一切使用せず、当該企業は本研究の計画・実施・解析・報告に関与することはない為、結果が有利に歪むことはない。また、データマネージメント、モニタリング、監査業務、統計を担当する者すべてが順天堂に所属しているが、参天製薬との利害関係は一切ない。

25　症例報告書（ＣＲＦ）の取り扱い

研究責任医師は、研究等の実施に係わる重要な文書（症例報告書（CRF）:研究の対象者ごとに医薬品等を用いた日時及び場所等に関する記録、研究計画書、実施計画、本研究の対象者に対する説明及びその同意に係る文書、総括報告書、認定臨床研究審査委員会から受け取った審査意見業務に係る文書、モニタリング及び監査に関する文書、本研究の実施に係る契約書、本研究に用いる医薬品等の概要を記載した文書、その他本研究を実施するために必要な文書）の保存については、研究の中止または終了後　5 年が経過した日までの間、各実施医療機関の研究責任医師が定める場所にて保存し、その後は個人情報に注意して廃棄する。CRF の取り扱い詳細に関しては、データマネジメントマニュアルに規定する。最終的な研究結果は順天堂大学に帰属する。

26　研究実施計画書の改訂

研究実施計画書に改訂の必要が生じた場合は、認定臨床研究審査委員会の定める手順に則って改訂する。

改訂の記録・理由などについては、表紙に示されている「更新・承認履歴一覧」に記載していく。

27　研究対象者等及びその関係者からの相談等への対応

この臨床研究に関する相談窓口を以下のとおり設ける。

【相談窓口】

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28　研究実施後における研究対象者への医療の提供に関する対応

研究終了後は、通常の保険診療での治療を継続する。

29 参考資料、文献リスト

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Clinical efficacy of diquafosol sodium 3% versus hyaluronic acid 0.1% in patients with dry eye disease after cataract surgery: a protocol for a single-center, randomized controlled trial

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Clinical efficacy of diquafosol sodium 3% versus hyaluronic acid 0.1% in patients with dry eye disease after cataract surgery: a protocol for a single-center, randomized controlled trial

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ABSTRACT

Introduction The number of cataract surgeries, the most common ophthalmic surgery, is expected to increase due to aging populations. Dry eye disease (DED) is a frequent side effect of cataract surgery, contributing to lower postoperative patient satisfaction and suboptimal quality of vision. It is unclear which eye drops commonly used in these patients should be recommended for postoperative DED treatment. This study aims to compare the efficacy of topical administration of diquafosol sodium 3% versus hyaluronic acid 0.1% eye drops in patients with DED after cataract surgery.

Methods and analysis The study is designed as a single-blind randomized controlled trial. The participants will be randomly (1:1) allocated to either the diquafosol sodium 3% topical administration group (n = 21) or the hyaluronic acid 0.1% topical administration group (n = 21). Each group will receive its assigned eye drop intervention over a 12-week period. The primary outcome will be measured using the total score of the Japanese version of the Ocular Surface Disease Index during the visit 5 weeks postoperatively. Both groups will be followed up after their respective eye drop application for 12 weeks according to the intervention regimens. Secondary outcome measures including meibomian gland function assessment, tear film break-up time, keratoconjunctival staining score, maximum blink interval, and tear secretion volume using Schirmer's test I will be assessed at 1, 5, 9, 13, and 25 weeks postoperatively.

Ethics and dissemination This study has been approved by the Juntendo Hospital Certified Review Board, Tokyo, Japan (Approved protocol V.7.0 dated 7 May 2021. Approval number: J20-018) and has been registered with the Japan Registry of Clinical Trials. Written informed consent will be collected from every patient prior to study participation. The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Trial registration number: jRCT1031210018

Strengths and limitations of this study

- This study will compare the efficacy of topical administration of diquafosol sodium 3% versus hyaluronic acid 0.1% eye drops in alleviating symptoms following cataract surgery in patients without preexisting dry eye disease (DED).
- The total number of participants will be 42 patients randomly allocated to the diquafosol sodium 3% (n = 21) or the hyaluronic acid 0.1% administration group (n = 21).
- Following the treatment over a 12-week period, the observation period from 13 to 24 weeks will be used to assess persistent eye drop effects and DED recurrence.
- The primary outcome will be measured using the total score of the Japanese version of the Ocular Surface Disease Index during the visit 5 weeks postoperatively.
- The generalizability of the findings of this study remains unknown since diquafosol sodium 3% and hyaluronic acid 0.1% are currently available in limited countries.

INTRODUCTION

The number of cataract surgeries, the most common ophthalmic surgery, is expected to increase due to aging populations worldwide.[1] Cataract surgery is generally recognized as a safe, reproducible, and effective procedure owing to improvements in surgical techniques and instruments.[2] Therefore, patients demand high postoperative quality of vision. Unfortunately, dry eye disease (DED) is a common disease, affecting approximately 5–50% of the population worldwide,[3] and a major cause of postoperative discomfort,[4] with recent studies revealing that cataract surgery is associated with the development and increased severity of dry eye symptoms.[5-8] In addition, DED has been shown to impair the quality of vision and increase economic losses due to reduced concentration and decreased work productivity stemming from a variety of DED-related symptoms, such as ocular discomfort and decreased visual acuity.[9, 10]

Importantly, contributory factors usually associated with DED differ from those implied in the development of DED after cataract surgery, which include the following: application of preoperative prophylactic medications; irritation of the ocular surface; application of topical anesthetics and antiseptics; intraoperative exposure to microscope light; corneal nerve transection; increased tear osmolarity; goblet cell loss; meibomian gland dysfunction; and surgery-related inflammation.[1, 5, 11-15] Moreover, numerous host factors including age, sex, presence of systemic diseases, administration of systemic medications, and preexisting DED or meibomian gland dysfunction are associated with the development of DED after cataract surgery.[1, 4, 5, 14, 16-23] The clinical presentation of postoperative DED caused by these factors is also different from that usually seen in DED, therefore, requiring a specialized treatment strategy for DED after cataract surgery.

Although the importance of DED management after cataract surgery has been recognized and many options to treat DED after cataract surgery have been developed,[1, 18-20, 24-34] the choice of treatment is left to the discretion of each physician, as no clear guidelines exist for the treatment of DED following cataract surgery. Diquafosol sodium 3% and hyaluronic acid 0.1% eye drops are two widely used medications in patients with DED.[35] There have been previous efforts to compare the effects of these eye drops after cataract surgery, and diquafosol sodium 3% produces significant improvement in the tear film break-up time and meibomian gland function.[20, 24, 36] However, these studies did not target the patients with newly developed DED after cataract surgery. This highlights the need to assess the efficacy of various eye drop medications in patients who develop DED following cataract surgery.[37, 38]

To the best of our knowledge, no report has yet compared the efficacy of diquafosol sodium 3% and hyaluronic acid 0.1% for DED after cataract surgery in patients without preexisting DED. Therefore, this study's objective is to compare the efficacy of these eye drops for DED after cataract surgery in such patients.

METHODS AND ANALYSIS

Objectives

The primary objective is to compare the efficacy of topical administrations of diquafosol sodium 3% versus hyaluronic acid 0.1% to alleviate dry eye symptoms

(measured using the Japanese version of the Ocular Surface Disease Index [J-OSDI]) after cataract surgery in patients without preexisting DED, as a therapy in addition to standard treatment following this operation.

Study design

The study is designed as a prospective, single-blind, randomized, controlled trial. The total number of participants will be 42 patients randomly allocated to the diquafosol sodium 3% administration group (n = 21) or the hyaluronic acid 0.1% administration group (n = 21). Each group will receive the assigned treatment over a 12-week period. A subsequent 12-week observation period from 13 to 24 weeks will be used to check for persistent eye drop effects and DED recurrence. The study design is depicted in figure 1.

Study setting

This study will be conducted between April 1st, 2021, and November 30th, 2025. Participants will be recruited at the Department of Ophthalmology, Juntendo University Hospital.[39]

Participant selection

This clinical trial will be conducted in a single center, with the participant blinded to the treatment allocation. Patients with DED after cataract surgery who attend the Department of Ophthalmology, Juntendo University Hospital, or are admitted there are eligible for inclusion in this study.

Inclusion criteria

1. Women who are 20 years of age or older at the time of providing informed consent.
2. Patients who have undergone cataract surgery in both eyes, with the second operation within 14 days after completion of the first.
3. Patients diagnosed with DED after cataract surgery (> 13 points total score in the J-OSDI and tear film break-up time ≤ 5 s), according to the 2016 Asia Dry Eye Society criteria.[40]
4. Patients who, after receiving a full explanation of their participation in the study and with a full understanding of the study, have given written consent to participate in the study of their own free will.
5. In case of inability to self-administer eye drops, patients with a caregiver willing and able to assist in the administration of the assigned eye drops as part of the study.

Exclusion criteria

1. Patients diagnosed with DED preoperatively.
2. Patients with active eye infections.
3. Venal keratoconjunctivitis patients.

4. Patients with recurrent corneal erosions.
5. Patients with hereditary corneal disease.
6. Patients with physical irritation of the cornea and conjunctiva due to eyelashes, tears, or conjunctivochalasis.
7. Patients who cannot or will not be able to discontinue eye drops and medications listed as prohibited concomitant drugs (including all prescription and over-the-counter medications), beginning with the start of the screening test until the end of the administration of the study medication.
8. Patients who cannot discontinue the use of contact lenses in the inclusion period, between the start of the screening test and the last administration of the eye drops.
9. Patients with a history of corneal refractive surgery.
10. Patients with punctal plugs or a history of surgical punctal occlusions.
11. Patients with hypersensitivity to components of the study drugs and reagents.
12. Patients using glaucoma eye drops.
13. Patients with systemic diseases, such as diabetes mellitus, thyroid disease, autoimmune diseases, and atopic dermatitis.
14. Patients whom the principal investigator deems unsuitable as a study participant.

Interventions

After enrollment in the study, participants will receive their corresponding study medication for the intervention period of 12 weeks after cataract surgery. The cataract surgery procedure entails an invasive corneal incision with a width of 2.4 mm. The conventional treatment is the administration of gatifloxacin 0.3% ophthalmic solution four times a day, betamethasone sodium phosphate 0.1% four times a day, and bromfenac sodium 0.1% twice a day up to 1 month after cataract surgery.

Arm A - diquafosol sodium 3% plus conventional treatment after cataract surgery
The participants will use diquafosol sodium 3% eye drops alongside conventional treatment after cataract surgery. Diquafosol sodium 3% is a P2Y2 receptor agonist that promotes tear fluid and mucin secretion.[41] Diquafosol sodium 3% eye drops will be administered six times a day.

Arm B - hyaluronic acid 0.1% plus conventional treatment after cataract surgery
The participants will use hyaluronic acid 0.1% eye drops alongside conventional treatment after cataract surgery. Hyaluronic acid is a glycosaminoglycan disaccharide linear biopolymer composed of repeating alternating sequences of N-acetyl-glucosamine and glucuronate.[42] Topical administration of hyaluronic acid 0.1% has been used to increase tear and mucin secretion on the ocular surface.[43] Hyaluronic acid 0.1% eye drops will be administered six times a day.

Outcome assessments

The schedule for data collection and visits is shown in table 1. Assessments will be performed following a predetermined sequence. After determining the subjective symptom score using the J-OSDI questionnaire, a physician will conduct a face-to-face medical examination and interview on lifestyle-related information. Following surgery,

a wide range of ophthalmic examinations will be performed, including measurements of corrected vision, intraocular pressure, contrast sensitivity, corneal curvature radius, and corneal endothelial cell density. In-person slit-lamp microscopy and fundoscopy examination by a physician will follow shortly after. The physician will continue with dry-eye-related ocular function tests and evaluate tear film break-up time, fluorescein staining score, maximum blink interval, and meibomian gland function. Subsequently, a trained nurse will measure the subject's tear production using Schirmer's test I. Patients will be provided with an individual patient diary that includes instructions for use, visit schedule, and how to use the eye drops. Patients' reports include the number of times eye drops were administered per day, reasons for not administering the eye drops, any side effects, and the use of new drugs other than the investigational drugs of this study.

Table 1 Schedule for data collection and visits

Periods	Pre-observation period		Drug administration period (12 weeks)				Post-administration period (12 weeks)
	Before cataract surgery	Cataract surgery	After cataract surgery				
	0–3 months before cataract surgery	Week 0	Week 1	Week 5	Week 9	Week 13	Week 25
Visit	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Informed consent and eligibility screening	○						
Registration to the study			○				
Randomization			○				
Participants' characteristics	○						
Lifestyle-related information	○		○	○	○	○	○
Ophthalmic examinations							
Visual acuity	○		○	○	○	○	○
Intraocular pressure	○		○	○	○	○	○
Contrast sensitivity	○		○	○	○	○	○
Keratometry	○		○	○	○	○	○
Endothelial cell count measurement	○		○	○	○	○	○
Slit-lamp microscopy	○		○	○	○	○	○
Fundus examination	○		○	○	○	○	○
Cataract surgery		○					
Postoperative eye drops for cataract surgery		○	○	○			

Information about cataract surgery		○				
Subjective symptoms of dry eye (J-OSDI)	○		○	○	○	○	○
Meibomian gland function assessment	○		○	○	○	○	○
Dry eye examination							
Tear film break-up time	○		○	○	○	○	○
Keratoconjunctival vital staining	○		○	○	○	○	○
Maximum blink interval	○		○	○	○	○	○
Tear secretion volume using Schirmer's test I	○		○	○	○	○	○
Treatment: diquafosol sodium 3% or hyaluronic acid 0.1%, 6 times per day			○	○	○	○	*
Adverse event collection			○	○	○	○	○
Patient diary		○	○	○	○	○	○

J-OSDI, Japanese version of the Ocular Surface Disease Index. *During the follow-up period, the treatment will be administrated when there is a recurrence of DED.

Primary outcome

Japanese version of the Ocular Surface Disease Index

The primary outcome measure will be the scores of the Ocular Surface Disease Index, which is a questionnaire consisting of 12 questions for evaluating the effects of dry eye syndrome on vision, ocular symptoms, and any condition associated with DED.[44] The J-OSDI, the Japanese version of this index, has been validated and will be used for this study.[45] The patient will answer each question on a scale ranging from 0 to 4, with 0 indicating 'none of the time' and 4 indicating 'all of the time'. If a certain question is deemed irrelevant, it will be marked as 'not applicable (N/A)' and excluded from the analysis. The J-OSDI total score is calculated according to the following formula.[44, 45]

$$\text{J}-\text{OSDI total score} = \frac{(\text{Sum of scores for all questions answered}) \times 100}{(\text{Total number of questions answered}) \times 4}$$

The scale ranges from 0 to 100, with higher scores representing more severe cases of DED. This value will be checked during visits preoperatively and 1, 5, 9, 13, and 25 weeks postoperatively.

Secondary outcomes

Secondary outcomes will be largely categorized into five groups: 1) general characteristics and relevant medical history, 2) lifestyle factors, 3) ophthalmic examination, 4) surgical information, and 5) ocular function tests.

Participants will provide characteristics including age, sex, diagnosis, and relevant medical history regarding the use of contact lenses, increased intraocular pressure, ocular surgery, corneal disease, mental illness, and hay fever. Information regarding lifestyle factors will contain self-reported headache, stiffness, screen time, sleep duration, exercise, smoking, and sleeping pills. Examination results on corrected visual acuity, intraocular pressure, contrast sensitivity, keratometry, endothelial cell count measurement, slit-lamp microscopy, and fundus examination will also be analyzed. Various surgical information that pertains to the cataract surgery, including surgical procedure, surgery time, complications, and information about the surgeon, will be collected for analysis.

Specific function test results on meibomian gland function and dry eye examinations will be collected and analyzed as well, including tear film break-up time (TFBUT), keratoconjunctival vital staining (CFS), maximum blink interval (MBI), and tear secretion volume according to the Schirmer's test I.

Outcomes that pertain to repeatable examinations or function tests will be measured during the preoperative visit, as well as during postoperative visits in weeks 1, 5, 9, 13, and 25.

Meibomian gland function assessment

Meibomian gland function will be assessed by applying digital pressure onto the lower central eyelid, in conjunction with slit-lamp microscopy according to the standard method.[46] Abnormal findings around the orifices are considered positive when at least one of three findings (irregular lid margin, vascular engorgement, and anterior or posterior replacement of the mucocutaneous junction) is recognized. Findings indicating orifice obstruction will be judged positive when both findings indicating meibomian gland orifice obstruction (plugging, pouting, and ridging, decreased meibomian secretion) are recognized.

Tear film break-up time

TFBUT will be measured using a fluorescein dye according to the standard method.[40] To minimize any effects of the test strip on tear volume and TFBUT, a small quantity of the dye will be administered with a wetted fluorescein strip. After the dye is instilled, the subject will be instructed to blink three times to ensure adequate mixing of the dye with the tears. The time interval between the last blink and the appearance of the first dark spot on the cornea will be measured with a stopwatch. The mean value of three measurements will be used. The cutoff value of TFBUT ≤ 5 s will be used to diagnose DED.[40]

Keratoconjunctival vital staining

CFS will be graded according to the van Bijsterveld grading system,[47] dividing the ocular surface into three zones: nasal bulbar conjunctiva, temporal bulbar conjunctiva, and cornea. Each zone will be evaluated on a scale of 0–3, with 0 indicating no staining and 3 indicating confluent staining. The maximum possible score is 9.

Maximum blink interval

MBI will be defined as the length of time that the participant can keep the eye open before blinking during each trial.[48] According to previous studies,[48, 49] using a stopwatch, MBI will be measured twice under a light microscope without light. MBI will be recorded as 30 s if it exceeds this value. The cutoff value of MBI ≤ 12.4 s will be used as a positive sign for DED.

Tear secretion volume using Schirmer's test I

Schirmer's test I will be performed without topical anesthesia after the completion of all other examinations. Schirmer test strips (Ayumi Pharmaceutical Co., Tokyo, Japan) will be placed at the outer third of the temporal lower conjunctival fornix for 5 min. The strips will be removed, and the length of dampened filter paper (in mm) will be recorded.

Participant timeline and trial duration

The schedule for data collection and visits is shown in Table 1. After registration for this study, the assigned treatment intervention will be administered for 12 weeks. Furthermore, the effect of eye drops and the recurrence of DED will be examined during the 12-week follow-up period 13–25 weeks after the surgery. During the follow-up period, the eye drops will be administered when DED recurs.

Randomization and allocation

Participants will be randomized to the diquafosol sodium 3% administration group or the hyaluronic acid 0.1% administration group. Randomization will be performed by a member of the trial team on the day of the visit 1 week after cataract surgery. A web-based randomization application will be used (https://www.project-redcap.org/). Allocation will be carried out using block randomization and stratified according to age (allocation factor: age < 80 years or ≥ 80 years). A randomization list for each stratum will be prepared by an independent statistician and will be stored in the university data center.

Masking

Study treatment assignment will be single masked. The study participants would be unable to identify the contents. Labels on the box containing the ampoules have a batch number, study reference number, participant ID, contact number, investigator name, site address, expiration date of the eye drops, storage instructions, and a statement informing the participant that the eye drops are for clinical trial use only and are not to be ingested.

Compliance

The study is to be conducted using an intention-to-treat basis. The level of compliance with eye drop use will be quantified based on the eye drop use calendar. There is no minimum compliance criterion for eye drop insertion that would cause the removal from the trial, but compliance will be controlled for in statistical analyses and used as a measure of acceptability of the treatment according to the secondary objectives. Evidence of overuse will also be discussed with participants, and they will be re-instructed on proper use and compliance.

Sample size and statistical analyses

The target number of cases is set at 42. The breakdown is as follows. First, a t-test for difference of means (power 0.8, significance level 5%, clinically valid difference in subjective symptom score 5.24,[24] standard deviation of the comparison group 5.23[24]) was used to determine a total of 34 cases in the two groups, with an additional 10% compensate since dry eye metrics often deviate from a normal distribution,[50] plus a 10% dropout rate for withdrawal of consent.

The study population for the efficacy analysis will be the intention-to-treat analysis population, which includes all randomized patients. In addition, a per-protocol set will be defined and analyzed to confirm the robustness of the study results.

The safety analysis will be conducted based on a safety analysis population that includes subjects who have received at least one dose of medication after randomization.

In this study, the level of significance is set at 5% two-sided, and the confidence coefficient is set at 95% unless otherwise specified. The study subject background will be tabulated by calculating the mean and standard deviation for continuous variables and the frequency and percentage for categorical variables. If the continuous variables do not follow a normal distribution, the variables will be appropriately transformed by logarithmic transformation or other means and aggregated with the mean and standard deviation, or the median and quartile range will be used as descriptive statistics.

For the primary endpoint, between-group comparisons will be performed with baseline as a covariate and an analysis of covariance to calculate the adjusted mean, its 95% confidence interval, and the *p*-value. Within-group comparisons will be made employing a paired t-test. For safety, frequencies and proportions will be calculated for each group and item, and between-group comparisons will be performed using Fisher's exact probability test or the χ^2 test.

Adverse events

Adverse events are unexpected signs, symptoms, or diseases encountered during the clinical trial, whether or not they are related to the treatment. Local, general, and psychological adverse events may be observed. Local symptoms may include corneal epithelium disorder (filamentary keratitis, superficial keratitis, corneal erosion, etc.), conjunctivitis, eye irritation, eye discharge, conjunctival hyperemia, eye pain, eye itching, ocular foreign body sensation, visual discomfort, hyposphagma, abnormal sensation in the eye (feeling of dry eyes, strange sensation of the eye, sticky eye sensation), blurred vision, photophobia, and lacrimation. If serious adverse events occur, these will be referred to the Juntendo Hospital Certified Review Board; experimental treatments will be stopped immediately, and appropriate treatments will be administered.

Participant withdrawal

Patients will be withdrawn from the study based on the following criteria:

1. When it is judged to be difficult to continue the research due to the occurrence of other diseases.
2. When the study participant becomes untraceable.
3. In the event of pregnancy or suspected pregnancy.
4. When participants or their guardians request to terminate their participation in the research.
5. When the participant’s caregiver cannot guarantee cooperation in the research.
6. When the research study is discontinued.
7. When the principal investigator and sub-investigators determine that it is appropriate

to discontinue the research for other reasons.

Data management

The principal investigator (Takenori Inomata) designated a person (Maria Miura, Juntendo University Faculty of Medicine, Department of Ophthalmology) to be in charge of the data management. This study uses REDCap as a case report form and management tool to collect data. Following database lock, the locked data will be transferred to the person in charge of statistical analysis. Details are specified in the data management manual. After the research is completed, a data management report will be prepared on the implementation and status of the data management, followed by its submission to the principal investigator along with the locked research data.

Limitations

First, the design of this study raises some concerns about confounding effects regarding the postoperative use of three types of eye drops: steroids, antibiotics, and anti-inflammatory drugs. For example, steroid eye drops can improve parameters associated with DED.[51] In addition, three of the postoperative eye drops used in this study contain preservatives. Preservatives may have an adverse effect on postoperative DED.[11, 18, 20] However, all patients in both groups will use the three postoperative eye drops in the same way. Therefore, differences between the two study groups are likely to be caused primarily by the tested eye drops for DED treatment. Second, the study based on this protocol will be a single-blind clinical trial and is not designed as a double-blind study, involving a risk of bias even when the researchers assess the study results as fairly as possible. Third, the sample size of this study is relatively small at 42, and the duration of eye drop implementation is relatively short at 12 weeks. A double-blind study with larger sample size and a longer treatment period could further validate the results of this study. In addition, we would only include women as participants to decrease the drop-out rate due to DED not developing following cataract surgery. Therefore, this study may have selection bias and cannot compare the effects of the eye drops on DED between the sexes. Finally, the generalizability of the findings of this study remains unknown since diquafosol sodium 3% and hyaluronic acid 0.1% are currently available in limited countries only.

ETHICS AND DISSEMINATION

Ethics

This study was approved by the Juntendo Hospital Certified Review Board, Tokyo, Japan (Approved protocol V.7.0 dated 7 May 2021. Approval number: J20-018) and was registered with the Japan Registry of Clinical Trials (jRCT; approval number: jRCT1031210018). Each participant will provide written informed consent prior to participation in the study.

Dissemination plan

The results of the study will be disseminated regardless of the direction of the effect. Trial results will be disseminated to all potential beneficiaries of the study, including patients, caregivers, relatives, physicians, advisory boards, and medical board members. This will take the form of publications in high-impact, open-access medical journals and presentations at national and international medical conferences.

PATIENT AND PUBLIC INVOLVEMENT

There was no direct patient or public involvement in this study.

DATA AVAILABILITY

All data relevant to the study are included in the article or uploaded as supplementary information.

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Contributors The study concept was conceived by TI. The design was conceived by MM, TI, SN, JSh, and MI. MM, TI, and JSu prepared the first draft of the manuscript. MM, TI, SN, JSu, MNag, and MI were involved in the drafting of the manuscript. JSh and AM provided critical advice to this study and edited the paper. All authors contributed to the critical revision of the manuscript and read and approved the final version.
MM, TI, YO, KFujio, YA, MK, TH, KH, and KFujim will conduct screening and data collection. The analysis will be performed by SN, JS, MNag, AMI, MNak, and MI.

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Competing interests Dr. Inomata reported receiving grants from Johnson & Johnson Vision Care, Inc., Hogy Medical Co, Ltd., SEED Co, Ltd., Santen Pharmaceutical Co, Ltd., Alcon Japan Ltd., Lion Ltd., and InnoJin Co, Ltd. and personal fees from Santen Pharmaceutical Co, Ltd., outside the submitted work. Dr. Murakami reported receiving grants from Eisai Co, Ltd., Kowa Ltd., Novartis Pharma K.K., HOYA Corporation, ROHTO Pharmaceutical Co, Ltd., Alcon Japan Ltd., AMO Japan K.K., Otsuka Pharmaceutical Co, Ltd., SEED Co, Ltd., Senju Pharmaceutical Co, Ltd., Novartis Pharma K.K., Pfizer Japan Inc, and Santen Pharmaceutical Co, Ltd. and personal fees from Johnson & Johnson Vision Care, Kowa Ltd., and Lion Ltd., outside the submitted work. No other disclosures were reported.

FIGURE LEGEND

Figure 1 Study schema.

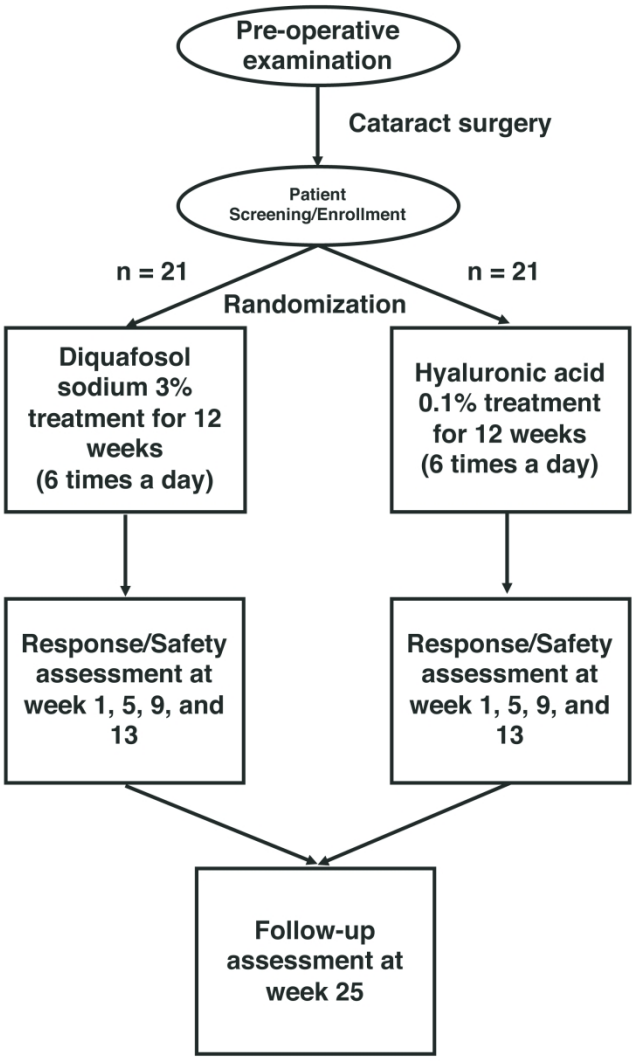
Pre-operative examination
Cataract surgery
Patient Screening/Enrollment
n = 21
n = 21
Randomization
Diquafosol sodium 3% treatment for 12 weeks (6 times a day)
Hyaluronic acid 0.1% treatment for 12 weeks (6 times a day)
Response/Safety assessment at week 1, 5, 9, and 13
Response/Safety assessment at week 1, 5, 9, and 13
Follow-up assessment at week 25

Figure 1

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1, 2, 3-13 17
Protocol version	3	Date and version identifier	1, 13
Funding	4	Sources and types of financial, material, and other support	17
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	17
	5b	Name and contact information for the trial sponsor	n/a
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	n/a
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3
	6b	Explanation for choice of comparators	4,5
Objectives	7	Specific objectives or hypotheses	3
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4,5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11,12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	5
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6-8

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10,11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	10
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	10
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	10
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	10
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	10
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10, 11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	13

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	10
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	11,12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	17
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Consent form
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.